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International application number: PCT/EP04/013539

International filing date: 29 November 2004 (29.11.2004)

Document type: Certified copy of priority document

Document details: Country/Office: EP  
Number: 04007447.8  
Filing date: 26 March 2004 (26.03.2004)

Date of receipt at the International Bureau: 18 January 2005 (18.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland  
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse



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**Patentanmeldung Nr.    Patent application No.    Demande de brevet n°**

04007447.8

Der Präsident des Europäischen Patentamts;  
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets  
p.o.

**R C van Dijk**







Anmeldung Nr:  
Application no.: 04007447.8  
Demande no:

Anmeldetag:  
Date of filing: 26.03.04  
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
Si aucun titre n'est indiqué se référer à la description.)

Protein complexes associated with the processing of the APP-protein

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s)  
revendiquée(s)  
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/  
Classification internationale des brevets:

C07K/

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of  
filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL  
PL PT RO SE SI SK TR LI



# PROTEIN COMPLEXES ASSOCIATED WITH THE PROCESSING OF APP-PROTEIN

## 1. FIELD OF THE INVENTION

The present invention relates to protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

## 2. BACKGROUND OF THE INVENTION

Alzheimer's disease is a chronic condition that affects millions of individuals worldwide. After onset of the disease sufferers require a high degree of supervision and care. As the proportion of aged individuals in the population increases, the number of sufferers of Alzheimer's disease is expected to expand dramatically. Current top drugs (e.g. Aricept®/donepezil) attempt to achieve a temporary improvement of cognitive functions by inhibiting acetylcholinesterase, which results in increased levels of the neurotransmitter acetylcholine in the brain. These therapies are not suitable for later stages of the disease, they do not treat the underlying disease pathology, and they do not halt disease progression. The growing need for an effective therapy, coupled with the absence of effective treatments, presents a significant opportunity for drug target development and drug discovery.

The brains of sufferers of Alzheimer's disease show a characteristic pathology of prominent neuropathologic lesions, such as the initially intracellular neurofibrillary tangles (NFTs), and the extracellular amyloid-rich senile plaques. These lesions are associated with massive loss of populations of CNS neurons and their progression accompanies the clinical dementia associated with AD. The major component of amyloid plaques is the amyloid beta peptide. Amyloid beta is the proteolytic product of a precursor protein, beta amyloid precursor protein (beta-APP or APP). APP is a type-I trans-membrane protein which is cleaved by several different membrane-associated proteases. The first cleavage of APP occurs extracellularly by one of two proteases, alpha-secretase or beta-secretase. Beta-secretase or BACE1 (beta-site APP-cleaving enzyme) is a type-I

transmembrane protein containing an aspartyl protease activity (described in detail below). Alpha secretase is a metalloprotease whose activity is most likely to be provided by one or a combination of the proteins ADAM10 and ADAM17. Following either the beta or alpha cleavage of APP, the final cleavage event occurs within the membrane and is carried out by a protein complex called gamma secretase. It is the combination of the beta and gamma secretase activities that results in the liberation of the Abeta peptides of 40 and 42 residues (there are also lower levels of other forms) from the APP and ultimately the formation of the amyloid plaques responsible for the pathology of Alzheimer's disease. It is believed that the Abeta-42 peptide is the most critical Abeta species, because it shows the most pronounced neurotoxicity, and can aggregate easily, thus forming a nucleus for the aggregation of other Abeta peptides, such as the Abeta-40 which is typically produced at higher levels than the other species.

The TAP-technology is particularly successful in the elucidation of membrane protein complexes. These multiprotein complexes form the core of the APP processing pathway and are not amenable to other techniques. Known proteins with an important functional role in APP processing were analysed with The applicant's technology to comprehensively chart the dynamic protein interactions that contribute to Abeta production. Selected novel targets are subsequently validated using cellular or biochemical assays. Moreover, purified multi-protein complexes (e.g. beta- or gamma-secretase) do represent defined functional molecular machines, which are used to evaluate the mechanism of known compounds and for the optimisation of leads.

### **Presenilins**

Presenilins 1 and 2 (PS1 and PS2) are integral membrane proteins which are localised in the endoplasmic reticulum, the Golgi and also at the cell surface [ Kovacs, D.M., et al., Alzheimer-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells. Nat Med, 1996. 2(2): p. 224-9.]. They are predominantly found as a heterodimers of the NTF and CTF endoproteolytic fragments. The protease that cleaves presenilins (the "presenilinase") is not known, it is likely that the process is autocatalytic, also the functional significance of PS (auto)proteolysis is unclear.

Presenilins are involved in the proteolytical processing of Amyloid precursor protein (APP) [ De Strooper, B., et al, Nature, 1998. 391(6665): p. 387-902] and the Notch receptor [ De Strooper, B., et al.,. Nature, 1999. 398(6727): p. 518-22., Ray, W.J., et al., . Proc Natl Acad Sci USA, 1999. 96(6): p. 3263-8.]. In addition, Presenilins are associated with the cell-adhesion proteins alpha and beta-catenin, N-cadherin, and E-cadherin [ Georgakopoulos, A., et al., Presenilin-1 forms complexes with the cadherin/catenin cell-cell adhesion system and is recruited to intercellular and synaptic contacts. Mol Cell, 1999. 4(6): p. 893-902] [ Zhang, Z., et al.,. Nature, 1998. 395(6703): p. 698-702.] and other members of the armadillo family [ Yu, G., et al., . J Biol Chem, 1998. 273(26): p. 16470-5] [ Zhou, J., et al.,. Neuroreport, 1997. 8(8): p. 2085-90] [ Levesque, G., et al.,. J Neurochem, 1999. 72(3): p. 999-1008.] [1 Tanahashi, H. and T. Tabira, . Neuroreport, 1999. 10(3): p. 563-8.

]APP processing by Presenilins is through their effects on gamma-secretase which cleaves APP, generating the C-terminus of the A-beta peptide. PS1 associates with the C83 and C99 processed C-terminal fragments of APP [1 Xia, W., et al.,. Proc Natl Acad Sci USA, 1997. 94(15): p. 8208-13.], Nicastrin [1 Yu, G., et al., Nature, 2000. 407(6800): p. 48-54] and Pen-2 [1 Francis, R., et al. Dev Cell, 2002. 3(1): p. 85-97]. Aph-1 [1 Francis, R., et al.,. Dev Cell, 2002. 3(1): p. 85-97] [1 Goutte, C., et al. Proc Natl Acad Sci U S A, 2002. 99(2): p. 775-9.] is required in Presenilin processing. It is not clear whether Presenilins regulate gamma-secretase activity directly or whether they are protease enzymes themselves Kopan, R. and A. Goate, . Genes Dev, 2000. 14(22): p. 2799-806. The gamma secretase activity could comprise a multimeric complex of these proteins [1 Yu, G., et al., . Nature, 2000. 407(6800): p. 48-54] [ Esler, W.P., et al., . Proc Natl Acad Sci U S A, 2002. 99(5): p. 2720-5.] but it is not known how the relationship between these proteins affects secretase activity.

Familial Alzheimer's disease (FAD) patients carry mutations in the presenilin proteins (PS1; PS2) or in APP. These mutations result in increased production of A-beta42 [1 Citron, M., et al.,. Nat Med, 1997. 3(1): p. 67-72.] which is the main component of cerebral plaques in FAD [ Jarrett, J.T., E.P. Berger, and P.T. Lansbury, Jr.,. Biochemistry, 1993. 32(18): p. 4693-7.].

Understanding the composition of the gamma-secretase complex, the relationship between its component parts and its regulation are important in the design of drugs for use in Alzheimer's disease patients.



### Nicastrin

Nicastrin is a type 1 trans-membrane glycoprotein with a conserved transmembrane domain and DYIGS motif [1 Yu, G., et al.,. *Nature*, 2000. 407(6800): p. 48-54] which is constitutively expressed in neural cell lines [Sato, J. and Y. Kuroda, . *Neuropathology*, 2001. 21(2): p. 115-22.]. Biochemical studies have shown that Nicastrin binds to Presenilins 1 and 2, C-terminal derivatives of APP [ Yu, G., et al.,. *Nature*, 2000. 407(6800): p. 48-54.], membrane-tethered forms of Notch [2 Chen, F., et al.. *Nat Cell Biol*, 2001. 3(8): p. 751-4.] and that it is a member of the gamma-secretase complex along with PS1 and PS2 [16]. Gamma secretase activity is involved in the cleavage of both Notch and APP. It has been shown that Nicastrin is required for the intra-membrane cleavage of Notch [ Lopez-Schier, H. and D. St Johnston, . *Dev Cell*, 2002. 2(1): p. 79-89.] and APP [ Chung, H.M. and G. Struhl,. *Nat Cell Biol*, 2001. 3(12): p. 1129-32], it may also have a role in post-translational stabilisation of Presenilin [ Hu, Y., Y. Ye, and M.E. Fortini, . *Dev Cell*, 2002. 2(1): p. 69-78].

Aph-1 [ Goutte, C., et al.,. *Proc Natl Acad Sci U S A*, 2002. 99(2): p. 775-9] and Pen-2 [ Francis, R., et al.,. *Dev Cell*, 2002. 3(1): p. 85-97.] were cloned recently in a screen for presenilin enhancers ("pen") in *C. elegans* and shown to interact genetically with Aph-2 (Nicastrin). Defects in Aph-1 affect Notch signalling and Nicastrin localisation [ Goutte, C., et al.,. *Proc Natl Acad Sci U S A*, 2002. 99(2): p. 775-9.]. Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins. Francis et al. [ Francis, R., et al., . *Dev Cell*, 2002. 3(1): p. 85-97] cloned the putative human orthologues of these genes, Aph-1a, Aph-1b and Pen-2, and recently Lee et al. [24] also cloned the human Aph-1 cDNAs.

The exact components of the gamma-secretase complex are not known but these two novel proteins could be components of or accessory factors to the complex and may interact together directly with Presenilin or with a Presenilin/Nicastrin complex. Nicastrin is therefore a member of the active gamma-secretase complex and there is recent evidence that it is the fully glycosylated form of the protein which is important in this complex. ( Leem, J.Y., et al., . *J Biol Chem*, 2002. 277: p. 19236-40, Tomita, T., et al., . *FEBS Lett*, 2002. 520(1-3): p. 117-21, Edbauer, D., et al., . *Proc Natl Acad Sci U S A*, 2002. 99(13): p. 8666-71, Yang, D.S., et al., . *J Biol Chem*, 2002. 277(31): p. 28135-42., Kimberly, W.T., et al.,. *J Biol Chem*, 2002. 277: p. 35113-7. ]

### **Aph-1**

Goutte et al. [ Goutte, C., et al., Proc Natl Acad Sci U S A, 2002. 99(2): p. 775-9] cloned aph-1 from *C. elegans*. Aph-1 encodes a novel conserved membrane protein with seven hydrophobic regions which are predicted to be membrane spanning. It has a 40 amino acid hydrophilic tail. *C. elegans* aph1 mutants have a phenotype which is indicative of a defect in Notch signalling. In these mutants, Aph-2 (Nicastrin) localisation is altered from being at the cell surface to being in the cytoplasm, concentrated around the nucleus. In *C. elegans*, Aph-1 interacts genetically with Aph-2 (Nicastrin) and Sel-12 (one of the *C. elegans* Presenilin genes) [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97].

There are Human, Mouse, *Drosophila* Aph-1 homologues which are potential orthologues. Recently, the human Aph-1 homologues, hAph-1a and hAph-1b have been cloned [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97,, Lee, S.F., et al., J Biol Chem, 2002. 23: p. 23.]. Aph-1a, the hypothetical CGI-78 protein, and Sambiasin-1 isolated by the applicant are all products of the same gene. Francis et al [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97.] showed that Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins in cultured *Drosophila* cells.

Lee et al. [ Lee, S.F., et al. J Biol Chem, 2002. 23: p. 23.] cloned two splice variants of Aph-1a called Aph-1aS and Aph-1aL and Aph-1b. They have shown that mammalian Aph-1aL associates with Nicastrin and PS1 NTF/CTF heterodimers and with PS2 and Nicastrin in cultured cells and that endogenous Aph1aL associates with Nicastrin and PS1 in rat brain. Inhibition of the expression of Aph1a reduces the expression of both PS1 and PS2 but not Nicastrin and results in the accumulation of gamma-secretase substrates and the reduction of Aβ<sub>42</sub>Aph1a was also shown to be required for Notch cleavage.

Aph-1 may have a role in the maturation and trafficking of Nicastrin but it is necessary for gamma-secretase function and may be a member of the gamma-secretase complex.

### **Pen-2**

Francis et al. [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97.] isolated pen-1 and pen-2 as two presenilin enhancer genes in a genetic screen in *C. elegans*. Pen-1 is identical to Aph-1 [ Goutte, C., et al., Proc Natl Acad Sci U S A, 2002. 99(2): p. 775-9.].



Pen-2 has two transmembrane domains and is thought to be a polytopic integral membrane protein. This group cloned the human homologues of Aph-1 and Pen-2. In *C. elegans*, Aph-1 and Pen-2 interact genetically with Aph-2 (Nicastrin) but not with each other. Hop-1 and Sel-12 are the *C. elegans* presenilin genes. Aph-2 interacts with Hop-1 whereas Aph-1 and Pen-2 interact with Sel-12 [ Francis, R., et al. *Dev Cell*, 2002. 3(1): p. 85-97.].

Pen-2 associates with PS1, PS2 and Nicastrin in mammalian cells and Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins in cultured *Drosophila* cells [ Francis, R., et al., . *Dev Cell*, 2002. 3(1): p. 85-97.].

Nicastrin maturation is affected by the levels of PS1 and Pen-2. Loss of PS1 or a reduction in expression of Nicastrin reduces Pen-2 protein levels and a reduction in expression of Pen-2 decreases levels of both PS1, PS2 proteins. In addition, reducing the expression of Pen-2 by RNAi reduces the level of the PS1 complex [ Steiner, H., et al.,. *J Biol Chem*, 2002: p. 39062-5]. These data suggest that Pen-2 is either a component of or regulates the assembly of the PS1 complex and that the expression of these proteins is co-ordinately regulated.

### **BACE1 (beta-secretase)**

Vassar et al. [ Vassar, R., et al., Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science*, 1999. 286(5440): p. 735-41.] cloned a transmembrane aspartic protease that had the characteristics of the postulated beta-secretase of APP. Three other groups also cloned BACE1 using different approaches. BACE1 knockout mice have a normal phenotype, suggesting that therapeutic inhibition of BACE1 for AD may be free of mechanism-based toxicity. BACE1 <sup>-/-</sup> mice who are also homozygous for an amyloid precursor protein transgene lack brain beta-amyloid and beta-secretase-cleaved APP C-terminal fragments. [ Roberds, S.L., et al., BACE knockout mice are healthy despite lacking the primary beta-secretase activity in brain: implications for Alzheimer's disease therapeutics. *Hum Mol Genet*, 2001. 10(12): p. 1317-24.

]. Brain and primary cortical cultures from BACE1 knockout mice showed no detectable beta-secretase activity, and primary cortical cultures from BACE knockout mice produced much less amyloid-beta from APP. This suggests that BACE1, rather than its paralogue BACE2, is the main beta-secretase for APP.

BACE1 is a protein of 501 amino acids containing a 21-aa signal peptide followed by a proprotein domain spanning aa 22 to 45. There are alternatively spliced forms, BACE-I-457 and BACE-I-476. The luminal domain of the mature protein is followed by one predicted transmembrane domain and a short cytosolic C-terminal tail of 24 aa. BACE1 is predicted to be a type 1 transmembrane protein with the active site on the luminal side of the membrane, where beta-secretase cleaves APP and possible other yet unidentified substrates. BACE1 mRNA in rat brain is present at higher levels in neurons than in glia, supporting that neurons are the primary source of the extracellular A-beta deposited in plaques. Sequence and mass spectrometry analyses showed that asn153, asn172, asn223, and asn354 of the BACE1 ectodomain are N-glycosylation sites. In addition, the ectodomain contains 6 cys residues that form disulfide bridges between positions 216 and 420, 278 and 443, and 330 and 380. The C-terminal domain of BACE1 contains a dileucine motif (LL499/500) that can potentially regulate its trafficking and endocytosis, and an adjacent serine, which is a casein kinase 1 phosphorylation site (S498) [ Huse, J.T., et al., Maturation and endosomal targeting of beta-site amyloid precursor protein-cleaving enzyme. The Alzheimer's disease beta-secretase. J Biol Chem, 2000. 275(43): p. 33729-37.

]. The propeptide is predominantly cleaved from BACE1 by furin [ Bennett, B.D., et al., A furin-like convertase mediates propeptide cleavage of BACE, the Alzheimer's beta -secretase. J Biol Chem, 2000. 275(48): p. 37712-7.]. In cells expressing wit or Swedish mutant APP, transient overexpression of BACE1 decreased alpha-secretase cleavage and increased beta-secretase activity at the known beta-secretase positions, asp1 and glu11. Although BACE1 is clearly a key enzyme required for the processing of APP into Ab, other potential substrates and functions of BACE1 are unknown. Also, no BACE1 interacting proteins with regulatory or modulatory functions have been described. Proteins that activate BACE1 activity would form suitable intervention points for Alzheimer's disease therapy. In addition, proteins that inhibit BACE1, like substrates or pseudosubstrates, could also provide suitable means of intervention e.g. as proteins therapeutics.

### APP

APP is the precursor of Abeta, a peptide which forms the principal component of Alzheimer disease (AD) senile plaques [ Masters, C.L., et al., Proc Natl Acad Sci U S A, 1985. 82(12): p. 4245-9.] Masters et al. purified the cerebral amyloid protein that forms

the plaque core in AD and Down syndrome. Van Nostrand et al. [ Van Nostrand, W.E., et al.,. *Nature*, 1989. 341(6242): p. 546-9.] presented evidence that nexin-II, a protease inhibitor that is synthesized and secreted by extravascular cells, is identical to APP. Multhaup et al. [ Multhaup, G., et al.,. *Science*, 1996. 271(5254): p. 1406-9.] demonstrated that APP is involved in copper reduction. They postulated that copper-mediated toxicity may contribute to neurodegeneration in AD, possibly by increased production of hydroxyl radicals. Yan et al. [ Yan, S.D., et al.,. *Nature*, 1996. 382(6593): p. 685-91.] reported that the receptor for advanced glycation end products RAGE is a receptor for the A-beta peptide and that expression of this receptor increases in AD. Expression of RAGE is particularly increased in neurons close to deposits of amyloid beta peptide and to neurofibrillary tangles. Kaneko et al. [ Kaneko, I., et al.,. *J Neurochem*, 1995. 65(6): p. 2585-93.] demonstrated that nanomolar concentrations of various synthetic beta amyloids specifically impaired mitochondrial succinate dehydrogenase, and speculated that one of the primary targets of beta amyloids is the mitochondrial electron transport chain.

Several missense mutations in the APP gene have been identified that result in early-onset AD: the Swedish APP670/671 double mutation; 3 different mutations at codon 717: the London APP717 mutation, V717I, V717F, and V717G; and the Florida APP716 mutation (Reviewed by Bertram and Tanzi [ Bertram, L. and R.E. Tanzi,. *J Mol Neurosci*, 2001. 17(2): p. 127-36.]). Most of these AD-related mutations involve amino acid changes near the beta- and gamma-secretase cleavage sites. Two other missense mutations in the APP gene are located within A-beta near the alpha-secretase cleavage site: the Flemish APP692 mutation, which is associated with cerebral hemorrhage due to congophilic amyloid angiopathy or with early-onset AD with onset age in the mid-forties; and the Dutch APP693 mutation. Almost all AD-linked mutations do elevate secretion of A-beta-42, however, APP693 does not. [ De Jonghe, C., et al.. *Neurobiol Dis*, 1998. 5(4): p. 281-6.]

Cao and Sudhof [ Cao, X. and T.C. Sudhof,. *Science*, 2001. 293(5527): p. 115-20] demonstrated that the cytoplasmic tail of APP forms a complex with the nuclear adaptor protein Fe65 and the histone acetyltransferase TIP60. This complex stimulates transcription via heterologous Gal4 or LexA DNA binding domains, suggesting that release of the cytoplasmic tail of APP by gamma-cleavage may function in gene expression. The complex could modify expression of genes that function in inflammation

[ Baek, S.H., et al.,. Cell, 2002. 110(1): p. 55-67] or apoptosis [ Kinoshita, A., et al.,. J Biol Chem, 2002. 277(32): p. 28530-6.].

Weggen et al. [ Weggen, S., et al.,. Nature, 2001. 414(6860): p. 212-6.] reported that the nonsteroidal antiinflammatory drugs ibuprofen, indomethacin, and sulindac can decrease the levels of high amyloidogenic amyloid-beta-42 peptide produced from a variety of cultured cells by as much as 80%. This effect was not seen in all NSAIDs and seemed not to be mediated by inhibition of cyclooxygenase (Cox) activity. Weggen et al. (2001) also demonstrated that short-term administration of ibuprofen to mice that produce APP lowered their brain levels of amyloid-beta-42. In cultured cells, the decrease in amyloid-beta-42 secretion was accompanied by an increase in the amyloid-beta(1-38) isoform, indicating that NSAIDs subtly alter gamma-secretase activity without significantly perturbing other APP processing pathways or Notch cleavage.

Proteins and other factors that regulate APP processing, and especially those that influence levels of Abeta-42 versus other Abeta species, form important potential targets in AD therapy.

### Tau

Neurofibrillary tangles (NFT), intraneuronal tau protein deposits, are hallmarks of several neurodegenerative disorders such as Alzheimer's and Pick's disease, frontotemporal dementia, cortico-basal degeneration and progressive supranuclear palsy.

The seven tau isoforms are all products of a single gene. Alternative splicing gives rise to six mRNA species differentially expressed in the CNS, depending on stage of neuronal maturation and neuron type. Tau is found mainly in the axon whereas a related protein, MAP2, is mainly found in dendrites.

Tau and MAP2 are microtubule-associated proteins (MAPs) which coassemble with microtubules and colocalise with microtubules in cells. Tau is a nonstructured molecule with a microtubule binding site containing 3 or 4 characteristic amino acid repeat in its carboxyl-terminal half. Alonso et al. [ Alonso, A.C., I. Grundke-Iqbal, and K. Iqbal,. Nat Med, 1996. 2(7): p. 783-7.] noted that in the brains of AD patients the neuronal cytoskeleton is progressively disrupted and replaced by tangles of paired helical filaments (PHFs), and that PHFs are composed mainly of hyperphosphorylated forms of tau. They demonstrated that in solution normal tau associated with the hyperphosphorylated AD P-tau to form large tangles of filaments. They also



demonstrated that dephosphorylation with alkaline phosphatase abolished the ability of AD P-tau to aggregate in vitro. In a form of autosomal dominant inherited dementia known as FTDP17 or Pick disease, the tau gene carries missense mutations or mutations in the 5'- splice site of exon 10, which results in increased levels of tau isoforms with 4 microtubule-binding repeats. These mutations lead to tau molecules that show reduced affinity for microtubules or are more prone to self aggregation.

Proteins and other factors that influence the affinity of tau protein for microtubules, and moreover, influence the aggregation of tau, which is probably mediated by phosphorylation and dephosphorylation events, are important potential targets in AD therapy.

### **X11beta**

X11beta/Mint-2 is a neuronal adaptor protein that is believed to be involved in signal transduction processes. It is also regarded as a putative vesicular trafficking protein in the brain that can form a complex with the potential to couple synaptic vesicle exocytosis to neuronal cell adhesion [ Biederer, T. and T.C. Sudhof,. J Biol Chem, 2000. 275(51): p. 39803-6.].

X11beta interacts with the Alzheimer's disease amyloid precursor protein (APP) [ McLoughlin, D.M. and C.C. Miller,. FEBS Lett, 1996. 397(2-3): p. 197-200.]. Acting synergistically with Munc18a [ Ho, C.S., et al.,. J Biol Chem, 2002. 277(30): p. 27021-8.], X11beta stabilises APP and inhibits production of proteolytic APP fragments including the A beta peptide that is deposited in the brains of Alzheimer's disease patients [ Sastre, M., R.S. Turner, and E. Levy,. J Biol Chem, 1998. 273(35): p. 22351-7.].

Via a mechanism that depends on its PDZ domain (yet has otherwise not been characterized), X11beta potently inhibits transactivation by an APP-Gal4/VP16 fusion protein [ Ho, C.S., et al.,. J Biol Chem, 2002. 277(30): p. 27021-8.]. Besides interacting with APP, X11beta binds to the C-terminus of presenilin1, although not as strongly as does X11alpha [ Ho, C.S., et al.,. J Biol Chem, 2002. 277(30): p. 27021-8.]. In addition, X11beta has been reported to interact with XB51 [ Lee, D.S., et al.,. J Biol Chem, 2000. 275(30): p. 23134-8.], but the functional significance of this interaction is unknown.

In *Drosophila*, dX11beta overexpression in eye imaginal disks causes disruption of compound eye morphology due to enhanced apoptosis of neuronal cells [ Hase, M., et al., J Neurochem, 2002. 81(6): p. 1223-32.]. X11beta has been shown to bind to NF-KappaB-p65 through its PDZ domain. This interaction has been implicated in NF-

KappaB-dependent Abeta42 production [ Tomita, S., et al., J Biol Chem, 2000. 275(17): p. 13056-60.].

Elucidation of X11beta complex composition and regulation might therefore help develop novel ways of therapeutic intervention in Alzheimer's disease and inflammation.

## **BACE2**

BACE2 is a glycosylated transmembrane protein of the aspartic protease family, constitutes the only paralog of BACE1, and was mapped to the Down's critical region of human chromosome ( Acquati, F., Accarino, M., Nucci, C., Fumagalli, P., Jovine, L., Ottolenghi, S., and Taramelli, R. (2000) FEBS Lett 468, 59-64, Solans, A., Estivill, X., and de La Luna, S. (2000) Cytogenet Cell Genet 89, 177-184, Farzan, M., Schnitzler, C. E., Vasilieva, N., Leung, D., and Choe, H. (2000) Proc Natl Acad Sci U S A 97, 9712-9717, Hussain, I., Powell, D. J., Howlett, D. R., Chapman, G. A., Gilmour, L., Murdock, P. R., Tew, D. G., Meek, T. D., Chapman, C., Schneider, K., Ratcliffe, S. J., Tattersall, D., Testa, T. T., Southan, C., Ryan, D. M., Simmons, D. L., Walsh, F. S., Dingwall, C., and Christie, G. (2000) Mol Cell Neurosci 16, 609-619). Both endoproteases share similar structural organization including a prodomain, a catalytic domain formed via DTG and DSG active site motifs, a single transmembrane domain, and a short C-terminal tail. BACE2 is expressed at low levels in most human peripheral tissues and at higher levels in colon, kidney, pancreas, placenta, prostate, stomach, and trachea. Human adult and fetal whole brain and most adult brain subregions express very low or undetectable levels of BACE2 mRNA ( Bennett, B. D., Babu-Khan, S., Loeloff, R., Louis, J. C., Curran, E., Citron, M., and Vassar, R. (2000) J Biol Chem 275, 20647-2065). BACE2 has a limited effect on the beta-secretase site but efficiently cleaves the sequences near the alpha-secretase site ( Yan, R., Munzner, J. B., Shuck, M. E., and Bienkowski, M. J. (2001) J Biol Chem 276, 34019-34027). BACE2 localizes in the endoplasmic reticulum, Golgi, trans-Golgi network, endosomes, and plasma membrane, and its cellular localization patterns depend on the presence of its transmembrane domain. BACE1 knockout mice are viable, possibly due to a redundancy in function with BACE2 ( Roberds, S. L., Anderson, J., Basi, G., Bienkowski, M. J., Branstetter, D. G., Chen, K. S., Freedman, S. B., Frigon, N. L., Games, D., Hu, K., Johnson-Wood, K., Kappenman, K. E., Kawabe, T. T., Kola, I., Kuehn, R., Lee, M., Liu, W., Motter, R., Nichols, N. F., Power, M., Robertson, D. W., Schenk, D., Schoor, M., Shopp, G. M., Shuck, M. E., Sinha, S.,

Svensson, K. A., Tatsuno, G., Tintrup, H., Wijsman, J., Wright, S., and McConlogue, L. (2001) *Hum Mol Genet* 10, 1317-1324).

Protein complexes involving BACE2 are of potential therapeutic value in AD therapy. The determination of the nature of the proteins interacting with and potentially regulating BACE1 but not BACE2 will constitute suitable therapeutic targets.

### Dab1

We have used mouse DAB1 because human Dab1 has not been cloned. Mutation in disabled-1 (Dab1) resemble mutations in reelin (Reln) by causing abnormalities in laminar structures throughout the brain and ataxia in reeler and scrambler mice ( Rice, D. S., Sheldon, M., D'Arcangelo, G., Nakajima, K., Goldowitz, D., and Curran, T. (1998) *Development* 125, 3719-3729). However, Reln and Dab1 are distinct in their molecular properties. Reln is a large extracellular protein secreted in the forebrain and the cerebellum. Dab1 is a cytoplasmic adapter protein that functions in phosphorylation-dependent intracellular signal transduction. It is suggested that Dab1 functions downstream of Reln in a signaling pathway that controls cell positioning in the developing brain ( Rice, D. S., Sheldon, M., D'Arcangelo, G., Nakajima, K., Goldowitz, D., and Curran, T. (1998) *Development* 125, 3719-3729). Reelin stimulates tyrosine kinases of the src family by a mechanism involving Dab1 ( Arnaud, L., Ballif, B. A., Forster, E., and Cooper, J. A. (2003) *Curr Biol* 13, 9-17 ). DAB1 has also been reported to interact with APP ( Trommsdorff, M., Borg, J. P., Margolis, B., and Herz, J. (1998) *Journal of Biological Chemistry* 273, 33556-33560) and with the cytoplasmic tails of LRP and LDL receptor (18). It was shown that Reln binds directly and specifically to the extracellular domains of VLDLR and ApoER2. Blockade of VLDLR and ApoER2 ligand binding correlated with loss of Reelin-induced Dab1 tyrosine phosphorylation. Mice lacking either Reln or VLDLR and ApoER2 show an increase in the phosphorylation level of tau proteins suggesting that Reln acts via Vldlr and ApoER2 to regulate Dab1 tyrosine phosphorylation and tau function in neurons ( Hiesberger, T., Trommsdorff, M., Howell, B. W., Goffinet, A., Mumby, M. C., Cooper, J. A., and Herz, J. (1999) *Neuron* 24, 481-489.). The functional role of the binding of Dab1 to the C-termini of APP, APLP1 and APLP2 has not been elucidated.

The protein complex around DAB1 is of high potential therapeutic interest for AD and related neurodegenerative diseases because it could provide further links of amyloid

pathology to downstream tangle pathology, and provide targets for the therapeutic modulation of the intracellular pathways leading to tau phosphorylation, tangle buildup, and neuronal death in AD.

### Fe65L2

Fe65 proteins are ligands of the cytoplasmic domain of APP ( Fiore, F., Zambrano, N., Minopoli, G., Donini, V., Duilio, A., and Russo, T. (1995) *J Biol Chem* 270, 30853-30856). The fe65 gene has two paralogues, Fe65L1 ( Guenette, S. Y., Chen, J., Jondro, P. D., and Tanzi, R. E. (1996) *Proc Natl Acad Sci U S A* 93, 10832-10837) and Fe65L2 ( Duilio, A., Faraonio, R., Minopoli, G., Zambrano, N., and Russo, T. (1998) *Biochem J* 330 ( Pt 1), 513-519). Fe65L2 encodes a protein of approx. 50 kDa which is expressed predominantly in brain and testis ( Tanahashi, H., Asada, T., and Tabira, T. (2002) *Ann Neurol* 52, 691-693). The three paralogues of the Fe65 protein family share three regions corresponding to the protein-protein interaction domains; the WW domain and the two PTB domains, whereas the remaining sequences are poorly related. Like Fe65, Fe65L1 and Fe65L2 genes encode two different protein isoforms, derived from the alternative splicing of a six nucleotide exon within the N-terminal PTB domain, in the presence or absence of two acidic/basic amino acids. Fe65 proteins have been found to translocate into the nucleus and to prevent the activation of the thymidylate synthase gene promoter induced by the transcription factor CP2 by an unknown mechanism ( Bruni, P., Minopoli, G., Brancaccio, T., Napolitano, M., Faraonio, R., Zambrano, N., Hansen, U., and Russo, T. (2002) *J Biol Chem* 277, 35481-35488).

Fe65L2 is able to interact, both in vitro and in vivo, with the intracellular domain of APP. Fe65 and Fe65L2 interact with APP, APLP1 and APLP2 with different efficiencies ( Duilio, A., Faraonio, R., Minopoli, G., Zambrano, N., and Russo, T. (1998) *Biochem J* 330 ( Pt 1), 513-519). Overexpression of Fe65L2 was reported to increase secretion of Abeta 1-40 and Abeta 1-42, however the molecular mechanism of this amyloidogenic effect is unknown. A c954C-->T polymorphism in the Fe65L2 gene is possibly associated with early-onset Alzheimer's disease (21). Fe65 proteins have been found to translocate into the nucleus and to prevent the activation of the thymidylate synthase gene promoter induced by the transcription factor CP2 by an unknown mechanism ( Bruni, P., Minopoli, G., Brancaccio, T., Napolitano, M., Faraonio, R., Zambrano, N., Hansen, U., and Russo,



T. (2002) J Biol Chem 277, 35481-35488). There are no interactors of Fe65L2 known that are not also found with Fe65.

The protein complex around Fe65L2 is of high potential therapeutic interest for AD and related neurodegenerative diseases because membrane-associated, cytoplasmic and nuclear complexes of the APP intracellular domain (AICD) with adaptor proteins regulate APP stability and turnover, nuclear translocation, and its transcriptional function, which are all potential targets for therapeutic intervention.

### **JIP1 (MAPK8IP1)**

The JIP proteins (40) function by scaffolding components of a MAP kinase module (including MLK, MKK7, and JNK) and facilitate signal transmission by the protein kinase cascade ( Yasuda, J., Whitmarsh, A. J., Cavanagh, J., Sharma, M., and Davis, R. J. (1999) Mol Cell Biol 19, 7245-7254).

Waeber et al. evaluated the role of JIP1 in beta-cells and proposed JIP-1 as a candidate gene for human diabetes. In one family a JIP1 missense mutation S59N segregated with diabetes and thus JIP1 represents a candidate susceptibility gene for type 2 diabetes ( Waeber, G., Delplanque, J., Bonny, C., Mooser, V., Steinmann, M., Widmann, C., Maillard, A., Miklossy, J., Dina, C., Hani, E. H., Vionnet, N., Nicod, P., Boutin, P., and Froguel, P. (2000) Nat Genet 24, 291-295).

Two groups presented evidence for an interaction of JIP1b with the cytoplasmic tail of APP ( Scheinfeld, M. H., Matsuda, S., and D'Adamio, L. (2003) Proc Natl Acad Sci U S A 100, 1729-1734, Scheinfeld, M. H., Roncarati, R., Vito, P., Lopez, P. A., Abdallah, M., and D'Adamio, L. (2002) J Biol Chem 277, 3767-3775., Matsuda, S., Yasukawa, T., Homma, Y., Ito, Y., Niikura, T., Hiraki, T., Hirai, S., Ohno, S., Kita, Y., Kawasumi, M., Kouyama, K., Yamamoto, T., Kyriakis, J. M., and Nishimoto, I. (2001) J Neurosci 21, 6597-6607.). Another group reported a mutual relationship of the expression levels of JIP1 and alpha synuclein in cultured neurons ( Hashimoto, M., Hsu, L. J., Rockenstein, E., Takenouchi, T., Mallory, M., and Masliah, E. (2002) J Biol Chem 277, 11465-11472.). Over-expression of JIP1 has been reported to stabilize immature APP and to suppress the production of an intracellular carboxyl-terminal fragment of APP (APP intracellular domain (AICD)), and the secretion of peptides A-beta 1-40 and A-beta 1-42, the predominant constituents of amyloid plaques in Alzheimer's disease. The mechanism of JIP1's amyloidogenic function is unknown. JIP1 and related proteins JIP2 and JIP3 bind

to the C-terminus of kinesin light chain suggesting that a JIP1-containing protein complex might be involved in APP trafficking ( Inomata, H., Nakamura, Y., Hayakawa, A., Takata, H., Suzuki, T., Miyazawa, K., and Kitamura, N. (2003) *J Biol Chem*, Verhey, K. J., Meyer, D., Deehan, R., Blenis, J., Schnapp, B. J., Rapoport, T. A., and Margolis, B. (2001) *J Cell Biol* 152, 959-970).

The protein complex around JIP1 is of high potential therapeutic interest for AD and related neurodegenerative diseases because membrane-associated, cytoplasmic and nuclear complexes of the APP intracellular domain (AICD) with adaptor proteins regulate APP stability and turnover, nuclear translocation, and its transcriptional function, which are all potential targets for therapeutic intervention.

### **FKRP**

Brockington et al. identified the fukutin-related protein gene (FKRP) by database screening using the mouse fukutin sequence and cloned fukutin-related protein (FKRP) by a combination of EST assembly, RT-PCR, and RACE ( Brockington, M., Blake, D. J., Prandini, P., Brown, S. C., Torelli, S., Benson, M. A., Ponting, C. P., Estournet, B., Romero, N. B., Mercuri, E., Voit, T., Sewry, C. A., Guicheney, P., and Muntoni, F. (2001) *Am J Hum Genet* 69, 1198-1209) . The cDNA encodes a 495-amino acid protein with a molecular organization similar to several Golgi-resident glycosyltransferases. Northern blot analysis detected a 4.0-kb FKRP transcript expressed predominantly in skeletal muscle, placenta, and heart and relatively weakly in other tissues.

FKRP mutations are found in families with severe and early-onset phenotypes of congenital muscular dystrophies (CMD). Structural brain defects, with or without mental retardation, are additional features of CMD. A variable reduction of alpha-dystroglycan expression was observed in the skeletal muscle biopsy of all individuals studied. In addition, several cases showed a deficiency of laminin 2 ( Brockington, M., Blake, D. J., Prandini, P., Brown, S. C., Torelli, S., Benson, M. A., Ponting, C. P., Estournet, B., Romero, N. B., Mercuri, E., Voit, T., Sewry, C. A., Guicheney, P., and Muntoni, F. (2001) *Am J Hum Genet* 69, 1198-1209, Brockington, M., Yuva, Y., Prandini, P., Brown, S. C., Torelli, S., Benson, M. A., Herrmann, R., Anderson, L. V., Bashir, R., Burgunder, J. M., Fallet, S., Romero, N., Fardeau, M., Straub, V., Storey, G., Pollitt, C., Richard, I., Sewry, C. A., Bushby, K., Voit, T., Blake, D. J., and Muntoni, F. (2001) *Hum Mol Genet* 10, 2851-2859).

FKRP and fukutin are Golgi-resident proteins and FKRP is required for the post-translational modification of dystroglycan ( Esapa, C. T., Benson, M. A., Schroder, J. E., Martin-Rendon, E., Brockington, M., Brown, S. C., Muntoni, F., Kroger, S., and Blake, D. J. (2002) *Hum Mol Genet* 11, 3319-3331).

FKRP is a novel interactor of PS1. Since exit of presenilins and the active gamma-secretase complex from the ER is critical for gamma-secretase function (52), FKRP and associated proteins may play a role in regulating gamma-secretase activity and/or trafficking, allowing access to APP. Interfering with FTRP and associated proteins may be a therapeutic strategy for the treatment of AD.

### **Protein Tyrosine Kinase 7 (PTK7)**

PTK7, also referred to as colon carcinoma kinase 4 (CCK4), is an immunoglobulin superfamily transmembrane glycoprotein related to chicken KLG and *D. melanogaster* off-track. The gene has been mapped to human chromosome 6p21.1-->p12.2 by fluorescence in situ hybridization (Banga et al., 1997, *Cytogenet Cell Genet.* 1997;76(1-2):43-4).

PTK7, several splicing variants of which exist in human tissues, differs from the receptor tyrosine kinase consensus sequence in several positions, suggesting that the protein be catalytically inactive (Mossie et al., 1995, *Oncogene.* 1995 Nov 16;11(10):2179-84.).

PTK7 is expressed in multiple human tissues, but its function is unknown. However, its similarity to the *D. melanogaster* transmembrane protein Off-track/Dtrk, which serves as a coreceptor of plexin A for semaphorins Sema 1A (Winberg et al., *Neuron.* 2001 Oct 11;32(1):53-62) and Sema 6D (Toyofuku et al., *Genes Dev.* 2004 Feb 15;18(4):435-47.), suggests that PTK7 might act as a coreceptor of a plexin-like protein. In the CNS, PTK7 might therefore play a role in maintenance of neuronal connectivity.

### **Glycogen Synthase Kinase 3a (GSK3a)**

GSK3a is a serine/threonine kinase that has been implicated in regulation of APP processing: RNA interference with GSK3a expression attenuates secretion of Abeta peptides (Phiel et al., 2003). Moreover, millimolar concentrations of lithium inhibit Abeta production both in-vitro and in-vivo. It has been suggested that GSK3a be the target that mediates lithium action in this context (Phiel et al, *Nature.* 2003 May 22;423(6938):435-

9). Since lithium blocks APP cleavage at the gamma-secretase step without interfering with Notch processing, GSK3a might constitute a suitable target for therapeutic intervention in AD.

### **Beta-Catenin (CtnnB1)**

Beta-catenin is a key player in the Wnt signaling pathway during embryonic patterning and cell-fate determination. Beta-catenin-containing nuclear protein complexes facilitate transcription of a broad range of target genes. Consequently, dysregulation of the Wnt pathway in general and beta-catenin in particular has been implicated in the pathogenesis of various types of cancer. Beta-catenin function is therefore tightly regulated by various effector proteins (van Es et al., *Curr Opin Genet Dev.* 2003 Feb;13(1):28-33).

Presenilin 1 binds to beta-catenin (Yu et al., *J Biol Chem.* 1998 Jun 26;273(26):16470-5.) and acts as a negative regulator of Wnt/beta-catenin signaling. Presenilin 1, containing familial AD mutations, destabilizes beta-catenin and potentiate neuronal apoptosis (Zhang et al., *Nature.* 1998 Oct 15;395(6703):698-702.). It has recently been proposed that presenilin 1 serves as a scaffold that promotes Wnt-independent phosphorylation and subsequent attenuation of beta-catenin-dependent transcription (Kang et al., *Cell.* 2002 Sep 20;110(6):751-62.). Loss of presenilin 1, in turn, is associated with enhanced beta-catenin signaling and skin tumorigenesis (Xia et al., *Proc Natl Acad Sci U S A.* 2001 Sep 11;98(19):10863-8.).

### **3. SUMMARY OF THE INVENTION**

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.



By applying the process according to the invention said complexes were identified. The components are listed in table 1.

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions;and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active

derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising the proteins selected from the proteins in table 1, third column or a homologue thereof, or a variant thereof or functionally active fragments or functionally active derivatives of said proteins, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions;  
wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, but 1 to the number of proteins listed in table 1, fifth column of said complex, or a homologue or a variant thereof, or a functionally active fragment or functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins of said fifth column under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm

DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the biochemical activity as stated in table 3.
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
Expressing a protein of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the protein, preferably a tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No.1 (a) and at least one of said proteins, being selected from the second group of proteins according to No.1 (b).
14. Host cell, containing a vector comprising a construct of No. 13 or containing several vectors each comprising at least the nucleic acid encoding at least one protein selected from the first group of proteins according to No.1 (a) and the nucleic acid encoding at least one protein selected from the second group of proteins according to No.1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of any of No.1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more containers the complex of any of No. 1 - 8, optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of a complex of any one of No. 1 - 8.
18. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
19. Array in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 17 is attached to a solid carrier.



20. A process for processing a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8.
22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders, preferentially for diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
23. A method for screening for a molecule that binds to the complex of any one of No. 1 - 8, comprising the following steps:
  - (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.
24. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:
  - (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.

25. The method of No. 24, wherein the amount of said complex is determined.
26. The method of No. 25, wherein the activity of said complex is determined.
27. The method of No. 25, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
28. The method of No. 24, wherein the amount of the individual protein components of said complex are determined.
29. The method of No. 25, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
30. The method of any of No. 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

32. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 24 - 29 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
33. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.
34. The method of No. 33, wherein the amount of said complex is determined.
35. The method of No. 33, wherein the activity of said complex is determined.
36. The method of No. 35, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
37. The method of No. 33, wherein the amount of the individual protein components of said complex are determined.
38. The complex of any one of No. 1 - 8 or the antibody or fragment of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder

such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity or, or protein components of, said complex.
40. The method according to No. 39, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
41. The method according to No. 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
42. Complex of No. 1 - 8 and/or any of the proteins listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

### 3.1 DEFINITIONS

The term "activity" as used herein, refers to the function of a molecule in its broadest sense. It generally includes, but is not limited to, biological, biochemical, physical or chemical functions of the molecule. It includes for example the enzymatic activity, the ability to interact with other molecules and ability to activate, facilitate, stabilize, inhibit, suppress or destabilize the function of other molecules, stability, ability to localize to certain subcellular locations. Where applicable, said term also relates to the function of a protein complex in its broadest sense.

The term "agonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, increases the amount of, or prolongs the



duration of, the activity of the complex. The stimulation may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Agonists may include proteins, nucleic acids, carbohydrates or any other organic or inorganic molecule or metals. Agonists also include a functional peptide or peptide fragment derived from a protein member of the complexes of the invention or a protein member itself of the complexes of the invention. Preferred activators are those which, when added to the complex and/or the protein of the invention under physiological conditions and/or in vitro assays, including diagnostic or prognostic assays, result in a change of the level of any of the activities of the protein complex and/or the proteins of the invention as exemplary illustrated above by at least 10%, at least 25%, at least 50%, at least 100%, at least, 200%, at least 500% or at least 1000% at a concentration of the activator  $1\mu\text{g ml}^{-1}$ ,  $10\mu\text{g ml}^{-1}$ ,  $100\mu\text{g ml}^{-1}$ ,  $500\mu\text{g ml}^{-1}$ ,  $1\text{mg ml}^{-1}$ ,  $10\text{mg ml}^{-1}$  or  $100\text{mg ml}^{-1}$ . Any combination of the above mentioned degrees of percentages and concentration may be used to define an agonist of the invention, with greater effect at lower concentrations being preferred.

The term "amount" as used herein and as applicable to the embodiment described relates to the amount of the particular protein or protein complex described, including the value of null, i.e. where no protein or protein complex described in that particular embodiment is present under the or any of the conditions which might be specified in that particular embodiment.

The term "animal" as used herein includes, but is not limited to mammals, preferably mammals such as cows, pigs, horses, mice, rats, cats, dogs, sheep, goats and most preferably humans. Other animals used in agriculture, such as chickens, ducks etc. are also included in the definition as used herein.

The term "animal" as used herein does not include humans if being used in the context of genetic alterations to the germline.

The term "antagonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, decreases the amount of, or the duration or level of activity of the complex. The effect may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Antagonists may include proteins, including antibodies, nucleic acids, carbohydrates or any other organic or inorganic molecule or metals. Antagonists also include a functional peptide or peptide fragment derived from a

protein member of the complexes of the invention or a protein member itself of the complexes of the invention. Preferred antagonists are those which, when added to the complex and/or the protein of the invention under physiological conditions and/or in vitro assays, including diagnostic or prognostic assays, result in a change of the level of any of the activities of the protein complex and/or the proteins of the invention as exemplary illustrated above by at least 10%, at least 20%, at least 30%, at least 40% at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99% at a concentration of the inhibitor of  $1\mu\text{g ml}^{-1}$ ,  $10\mu\text{g ml}^{-1}$ ,  $100\mu\text{g ml}^{-1}$ ,  $500\mu\text{g ml}^{-1}$ ,  $1\text{mg ml}^{-1}$ ,  $10\text{mg ml}^{-1}$  or  $100\text{mg ml}^{-1}$ .

Any combination of the above mentioned degrees of percentages and concentration may be used to define antagonist of the invention, with greater effect at lower concentrations being preferred.

The term "antibodies" as used herein, include include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library.

The term "binding" as used herein means a stable or transient association between two molecules, including electrostatic, hydrophobic, ionic and/or hydrogen-bond interaction under physiological conditions and/or conditions being used in diagnostic or prognostic method or process or procedure.

The term "carrier" as used herein refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional

binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

If not stated otherwise, the terms "complex" and "protein complex" are used interchangeably herein and refer to a complex of proteins that is able to perform one or more functions of the wild type protein complex. The protein complex may or may not include and/or be associated with other molecules such as nucleic acid, such as RNA or DNA, or lipids or further cofactors or moieties selected from a metal ions, hormones, second messengers, phosphate, sugars.

A "complex" of the invention may also be part of or a unit of a larger physiological protein assembly.

The term "component of the APP processing pathway" as used herein refers to a protein and/or protein complex which is involved in mediating APP processing in a cell. Components of the APP processing pathway include the following protein complexes as provided herein and components thereof:

BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastrin-complex, Aph-1a, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRFP-complex, PTK7-complex.

If not stated otherwise, the term "compound" as used herein are include but are not limited to peptides, nucleic acids, carbohydrates, natural product extract librariesorganic molecules, preferentially small organic molecules, anorganic molecules, including but not limited to chemicals, metals and organometallic molecules.

The terms "derivatives" or "analogs of component proteins" or "variants" as used herein include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done



by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions. It means a protein which is the outcome of a modification of the naturally occurring protein, by amino acid substitutions, deletions and additions, respectively, which derivatives still exhibit the biological function of the naturally occurring protein although not necessarily to the same degree. The biological function of such proteins can e.g. be examined by suitable available in vitro assays as provided in the invention.

The term "functionally active" as used herein refers to a polypeptide, namely a fragment or derivative, having structural, regulatory, or biochemical functions of the protein according to the embodiment of which this polypeptide, namely fragment or derivative is related to.

The term "fragment" as used herein refers to a polypeptide of at least 10, 20, 30, 40 or 50 amino acids of the component protein according to the embodiment. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids.

The term "gene" as used herein refers to a nucleic acid comprising an open reading frame encoding a polypeptide of, if not stated otherwise, the present invention, including both exon and optionally intron sequences.

The terms "homologue" or "homologous gene products" as used herein mean a protein in another species, preferably mammals, which performs the same biological function as the a protein component of the complex further described herein. Such homologues are also termed "orthologous gene products". The algorithm for the detection of orthologue gene pairs from humans and mammals or other species uses the whole genome of these organisms. First, pairwise best hits are retrieved, using a full Smith-Waterman alignment of predicted proteins. To further improve reliability, these pairs are clustered with pairwise best hits involving *Drosophila melanogaster* and *C. elegans* proteins. Such analysis is given, e.g., in Nature, 2001, 409:860-921. The homologues of the proteins according to the invention can either be isolated based on the sequence homology of the genes encoding the proteins provided herein to the genes of other species by cloning the respective gene applying conventional technology and expressing the protein from such gene, or by isolating proteins of the other species by isolating the analogous complex according to the methods provided herein or to other suitable methods commonly known in the art.



The term "host cells" or, where applicable, "cells" or "hosts" as used herein is intended to be understood in a broadest sense and include, but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used. It is understood that this term not only refers to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The term "modification" as used herein refers to all modifications of a protein or protein complex of the invention including cleavage and addition or removal of a group.

The term "nucleic acid" as used herein refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). They may also be polynucleotides which include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphorothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. For the purposes of the present invention, it is to be understood that the polynucleotides described herein may be modified by any method available in the art. Such modifications may be carried out in order to enhance the *in vivo* activity or lifespan of polynucleotides of the invention. Polynucleotides according to the invention may be produced recombinantly, synthetically, or by any means available to those of skill in the art. They may also be cloned by standard techniques. The polynucleotides are typically provided in isolated and/or purified form. As applicable to the embodiment being described, they include both single stranded and double-stranded polynucleotides.

The term "percent identity", as used herein, means the number of identical residues as defined by an optimal alignment using the Smith-Waterman algorithm divided by the length of the overlap multiplied by 100. The alignment is performed by the search program (Pearson, 1991, *Genomics* 11:635-650) with the constraint to align the maximum of both sequences.

The terms "polypeptides" and "proteins" are, where applicable, used interchangeably herein. They may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated or comprise modified amino acid residues. They may also be modified by the addition of a signal sequence to promote their secretion from a cell where the polypeptide does not naturally contain such a sequence. They may be tagged with a tag. They may be tagged with different labels which may assist in identification of the proteins in a protein complex. Polypeptides/proteins for use in the invention may be in a substantially isolated form. It will be understood that the polypeptide/protein may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated. A polypeptide/protein for use in the invention may also be in a substantially purified form, in which case it will generally comprise the polypeptide in a preparation in which more than 50%, e.g. more than 80%, 90%, 95% or 99%, by weight of the polypeptide in the preparation is a polypeptide of the invention.

"Target for therapeutic drug" means that the respective protein (target) can bind the active ingredient of a pharmaceutical composition and thereby changes its biological activity in response to the drug binding.

The term "tag" as used herein is meant to be understood in its broadest sense and to include, but is not limited to any suitable enzymatic, fluorescent, or radioactive labels and suitable epitopes, including but not limited to HA-tag, Myc-tag, T7, His-tag, FLAG-tag, Calmodulin binding proteins, glutathione-S-transferase, strep-tag, KT3-epitope, EEF-epitopes, green-fluorescent protein and variants thereof.

The term "therapeutics" as used herein, includes, but is not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments); antibodies thereto; nucleic acids encoding the component protein, and analogs or derivatives thereof; component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The term "vector" as used herein means a nucleic acid molecule capable of transporting another nucleic acid sequence to which it has been linked. Preferred vectors are those capable of autonomous replication and/or expression of nucleic acids to which they are linked. The terms "plasmid" and "vector" are used interchangeably herein when applicable to the embodiment. However, vectors other than plasmids are also included herein. The expression elements of vectors vary in their strengths and specificities.

Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

#### 4. DETAILED DESCRIPTION OF THE INVENTION

##### Overview:

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said protein complex were identified. The components are listed in table 1.

Said object is further achieved by the characterisation of component proteins. These proteins are listed in table 2.

The invention thus relates to the following embodiments:

4. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions;and a complex (II) comprising at least two of said second proteins,

wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

5. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
6. A protein complex comprising the proteins selected from the proteins in table 1, third column or a homologue thereof, or a variant thereof or functionally active fragments or functionally active derivatives of said proteins, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions;  
wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM



Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, but 1 to the number of proteins listed in table 1, fifth column of said complex, or a homologue or a variant thereof, or a functionally active fragment or functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins of said fifth column under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

30. The complex of any of No. 1 - 7 that is involved in the biochemical activity as stated in table 3.
31. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
Expressing a protein of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the protein, preferably a tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
32. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
33. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
34. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
35. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No.1 (a) and at least one of said proteins, being selected from the second group of proteins according to No.1 (b).
36. Host cell, containing a vector comprising a construct of No. 13 or containing several vectors each comprising at least the nucleic acid encoding at least one protein selected from the first group of proteins according to No.1 (a) and the nucleic acid encoding at least one protein selected from the second group of proteins according to No.1 (b).



37. An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
38. A kit comprising in one or more containers the complex of any of No. 1 - 8, optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
39. The kit according to No. 16 for processing a substrate of a complex of any one of No. 1 - 8.
40. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
41. Array in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 17 is attached to a solid carrier.
42. A process for processing a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
43. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8.
44. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders, preferentially for diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
45. A method for screening for a molecule that binds to the complex of any one of No. 1 - 8, comprising the following steps:
  - (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

46. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:
- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.
47. The method of No. 24, wherein the amount of said complex is determined.
48. The method of No. 25, wherein the activity of said complex is determined.
49. The method of No. 25, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
50. The method of No. 24, wherein the amount of the individual protein components of said complex are determined.

51. The method of No. 25, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
30. The method of any of No. 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 24 - 29 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous

sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.

34. The method of No. 33, wherein the amount of said complex is determined.
35. The method of No. 33, wherein the activity of said complex is determined.
36. The method of No. 35, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
37. The method of No. 33, wherein the amount of the individual protein components of said complex are determined.
38. The complex of any one of No. 1 - 8 or the antibody of fragment of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity or, or protein components of, said complex.
40. The method according to No. 39, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.



41. The method according to No. 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
42. Complex of No. 1 - 8 and/or any of the proteins listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

Animal models are also provided herein.

Preferably, the protein components of the complexes described herein are all mammalian proteins. The complexes can also consist only of the respective homologues from other mammals such as mouse, rat, pig, cow, dog, monkey, sheep or horse or other species such as *D. melanogaster*, *C. elegans* or chicken. In another preferred embodiment, the complexes are a mixture of proteins from two or more species.

#### TABLES:

##### Table 1: Composition of Complexes

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Entry point'): Lists the bait proteins that have been chosen for the purification of the given complex.

Third column ('All interactors'): Lists all novel interactors which have been identified as members of the complex and all interactors which have been known to be associated with the bait so far.

Fourth column ('Known interactors'): Lists all interactors which have been known to be associated with the bait so far.

Fifth column ('Novel interactors of the complex'): Lists all novel interactors of the complex which have been identified in the experiments provided herein.

##### Table 2: Individual Proteins of the Complexes

First column ('Protein'): Lists in alphabetical order all proteins which have been identified as interactors of the complexes presented herein.

Second column ('SEQ. ID'): Lists the SEQ ID (Sequence Identifications) of the proteins herein as used herein.

Third column ('IPI-Numbers'): Lists the IPI-Numbers of the proteins herein. The IPI-Numbers refer to the International Protein Index created by the European Bioinformatics Institute (EMBL-EBI), Hinxton, UK.

Fourth column ('Molecular Weight'): Lists the Molecular Weight of the proteins in Dalton.

Table 3: Biochemical Activities of the Complexes of the invention.

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Biochemical Activity'): Lists biochemical activities of the complexes. Assays in order to test these activities are also provided herein (infra).

#### 4.1 PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The protein complexes of the present invention and their component proteins are described in the Tables 1 - 3. The protein complexes and component proteins can be obtained by methods well known in the art for protein purification and recombinant protein expression. For example, the protein complexes of the present invention can be isolated using the TAP method described in Section 5, infra, and in WO 00/09716 and Rigaut et al., 1999, Nature Biotechnol. 17:1030-1032, which are each incorporated by reference in their entirety. Additionally, the protein complexes can be isolated by immunoprecipitation of the component proteins and combining the immunoprecipitated proteins. The protein complexes can also be produced by recombinantly expressing the component proteins and combining the expressed proteins.

The nucleic and amino acid sequences of the component proteins of the protein complexes of the present invention are provided herein (SEQ ID NO 1 - 152), and can be obtained by any method known in the art, e.g., by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of each sequence, and/or by cloning from a cDNA or genomic library using an oligonucleotide specific for each nucleotide sequence.

Homologues (e.g., nucleic acids encoding component proteins from other species) or other related sequences (e.g., variants, paralogs) which are members of a

native cellular protein complex can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular nucleic acid sequence as a probe, using methods well known in the art for nucleic acid hybridization and cloning.

Exemplary moderately stringent hybridization conditions are as follows: prehybridization of filters containing DNA is carried out for 8 hours to overnight at 65°C in buffer composed of 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500  $\mu$ g/ml denatured salmon sperm DNA. Filters are hybridized for 48 hours at 65°C in prehybridization mixture containing 100  $\mu$ g/ml denatured salmon sperm DNA and 5-20  $\times 10^6$  cpm of  $^{32}$ P-labeled probe. Washing of filters is done at 37°C for 1 hour in a solution containing 2X SSC, 0.01% PVP, 0.01% Ficoll, and 0.01% BSA. This is followed by a wash in 0.1X SSC at 50 °C for 45 min before autoradiography. Alternatively, exemplary conditions of high stringency are as follows: e.g., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel et al., eds., 1989, Current Protocols in Molecular Biology, Vol. 1, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3). Other conditions of high stringency which may be used are well known in the art. Exemplary low stringency hybridization conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100  $\mu$ g/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

For recombinant expression of one or more of the proteins, the nucleic acid containing all or a portion of the nucleotide sequence encoding the protein can be inserted into an appropriate expression vector, i.e., a vector that contains the necessary elements for the transcription and translation of the inserted protein coding sequence. The necessary transcriptional and translational signals can also be supplied by the native promoter of the component protein gene, and/or flanking regions.

A variety of host-vector systems may be utilized to express the protein coding sequence. These include but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression

elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

In a preferred embodiment, a complex of the present invention is obtained by expressing the entire coding sequences of the component proteins in the same cell, either under the control of the same promoter or separate promoters. In yet another embodiment, a derivative, fragment or homologue of a component protein is recombinantly expressed. Preferably the derivative, fragment or homologue of the protein forms a complex with the other components of the complex, and more preferably forms a complex that binds to an anti-complex antibody. Such an antibody is further described infra.

Any method available in the art can be used for the insertion of DNA fragments into a vector to construct expression vectors containing a chimeric gene consisting of appropriate transcriptional/translational control signals and protein coding sequences. These methods may include in vitro recombinant DNA and synthetic techniques and in vivo recombinant techniques (genetic recombination). Expression of nucleic acid sequences encoding a component protein, or a derivative, fragment or homologue thereof, may be regulated by a second nucleic acid sequence so that the gene or fragment thereof is expressed in a host transformed with the recombinant DNA molecule(s). For example, expression of the proteins may be controlled by any promoter/enhancer known in the art. In a specific embodiment, the promoter is not native to the gene for the component protein. Promoters that may be used can be selected from among the many known in the art, and are chosen so as to be operative in the selected host cell.

In a specific embodiment, a vector is used that comprises a promoter operably linked to nucleic acid sequences encoding a component protein, or a fragment, derivative or homologue thereof, one or more origins of replication, and optionally, one or more selectable markers (e.g., an antibiotic resistance gene).

In another specific embodiment, an expression vector containing the coding sequence, or a portion thereof, of a component protein, either together or separately, is made by subcloning the gene sequences into the EcoRI restriction site of each of the three pGEX vectors (glutathione S-transferase expression vectors; Smith and Johnson, 1988, *Gene* 7:31-40). This allows for the expression of products in the correct reading frame.



Expression vectors containing the sequences of interest can be identified by three general approaches: (a) nucleic acid hybridization, (b) presence or absence of "marker" gene function, and (c) expression of the inserted sequences. In the first approach, coding sequences can be detected by nucleic acid hybridization to probes comprising sequences homologous and complementary to the inserted sequences. In the second approach, the recombinant vector/host system can be identified and selected based upon the presence or absence of certain "marker" functions (e.g., resistance to antibiotics, occlusion body formation in baculovirus, etc.) caused by insertion of the sequences of interest in the vector. For example, if a component protein gene, or portion thereof, is inserted within the marker gene sequence of the vector, recombinants containing the encoded protein or portion will be identified by the absence of the marker gene function (e.g., loss of  $\beta$ -galactosidase activity). In the third approach, recombinant expression vectors can be identified by assaying for the component protein expressed by the recombinant vector. Such assays can be based, for example, on the physical or functional properties of the interacting species in in vitro assay systems, e.g., formation of a complex comprising the protein or binding to an anti-complex antibody.

Once recombinant component protein molecules are identified and the complexes or individual proteins isolated, several methods known in the art can be used to propagate them. Using a suitable host system and growth conditions, recombinant expression vectors can be propagated and amplified in quantity. As previously described, the expression vectors or derivatives which can be used include, but are not limited to, human or animal viruses such as vaccinia virus or adenovirus; insect viruses such as baculovirus, yeast vectors; bacteriophage vectors such as lambda phage; and plasmid and cosmid vectors.

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies or processes the expressed proteins in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically-engineered component proteins may be controlled. Furthermore, different host cells have characteristic and specific mechanisms for the translational and post-translational processing and modification (e.g., glycosylation, phosphorylation, etc.) of proteins. Appropriate cell lines or host systems can be chosen to ensure that the desired modification and processing of the foreign protein is achieved. For example, expression in a bacterial system can be used to produce an unglycosylated core protein, while expression in mammalian cells ensures

"native" glycosylation of a heterologous protein. Furthermore, different vector/host expression systems may effect processing reactions to different extents.

In other specific embodiments, a component protein or a fragment, homologue or derivative thereof, may be expressed as fusion or chimeric protein product comprising the protein, fragment, homologue, or derivative joined via a peptide bond to a heterologous protein sequence of a different protein. Such chimeric products can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acids to each other by methods known in the art, in the proper coding frame, and expressing the chimeric products in a suitable host by methods commonly known in the art. Alternatively, such a chimeric product can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Chimeric genes comprising a portion of a component protein fused to any heterologous protein-encoding sequences may be constructed.

In particular, protein component derivatives can be made by altering their sequences by substitutions, additions or deletions that provide for functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other DNA sequences that encode substantially the same amino acid sequence as a component gene or cDNA can be used in the practice of the present invention. These include but are not limited to nucleotide sequences comprising all or portions of the component protein gene that are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Likewise, the derivatives of the invention include, but are not limited to, those containing, as a primary amino acid sequence, all or part of the amino acid sequence of a component protein, including altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity that acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and

histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

In a specific embodiment, up to 1%, 2%, 5%, 10%, 15% or 20% of the total number of amino acids in the wild type protein are substituted or deleted; or 1, 2, 3, 4, 5, or 6 or up to 10 or up to 20 amino acids are inserted, substituted or deleted relative to the wild type protein.

In a specific embodiment of the invention, the nucleic acids encoding a protein component and protein components consisting of or comprising a fragment of or consisting of at least 6 (continuous) amino acids of the protein are provided. In other embodiments, the fragment consists of at least 10, 20, 30, 40, or 50 amino acids of the component protein. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids. Derivatives or analogs of component proteins include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions.

In a specific embodiment, proteins are provided herein, which share an identical region of 20, 30, 40, 50 or 60 contiguous amino acids of the proteins listed in table 2.

The protein component derivatives and analogs of the invention can be produced by various methods known in the art. The manipulations which result in their production can occur at the gene or protein level. For example, the cloned gene sequences can be modified by any of numerous strategies known in the art (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York). The sequences can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated in vitro. In the production of the gene encoding a derivative, homologue or analog of a component protein, care should be taken to ensure that the modified gene retains the original translational reading frame, uninterrupted by translational stop signals, in the gene region where the desired activity is encoded.

Additionally, the encoding nucleic acid sequence can be mutated in vitro or in vivo, to create and/or destroy translation, initiation, and/or termination sequences, or to



create variations in coding regions and/or form new restriction endonuclease sites or destroy pre-existing ones, to facilitate further in vitro modification. Any technique for mutagenesis known in the art can be used, including but not limited to, chemical mutagenesis and in vitro site-directed mutagenesis (Hutchinson et al., 1978, J. Biol. Chem. 253:6551-6558), amplification with PCR primers containing a mutation, etc.

Once a recombinant cell expressing a component protein, or fragment or derivative thereof, is identified, the individual gene product or complex can be isolated and analyzed. This is achieved by assays based on the physical and/or functional properties of the protein or complex, including, but not limited to, radioactive labeling of the product followed by analysis by gel electrophoresis, immunoassay, cross-linking to marker-labeled product, etc.

The component proteins and complexes may be isolated and purified by standard methods known in the art (either from natural sources or recombinant host cells expressing the complexes or proteins), including but not restricted to column chromatography (e.g., ion exchange, affinity, gel exclusion, reversed-phase high pressure, fast protein liquid, etc.), differential centrifugation, differential solubility, or by any other standard technique used for the purification of proteins. Functional properties may be evaluated using any suitable assay known in the art.

Alternatively, once a component protein or its derivative, is identified, the amino acid sequence of the protein can be deduced from the nucleic acid sequence of the chimeric gene from which it was encoded. As a result, the protein or its derivative can be synthesized by standard chemical methods known in the art (e.g., Hunkapiller et al., 1984, Nature 310:105-111).

Manipulations of component protein sequences may be made at the protein level. Included within the scope of the invention is a complex in which the component proteins or derivatives and analogs that are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease,  $\text{NaBH}_4$ , acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc.

In specific embodiments, the amino acid sequences are modified to include a fluorescent label. In another specific embodiment, the protein sequences are modified to



have a heterofunctional reagent; such heterofunctional reagents can be used to crosslink the members of the complex.

In addition, complexes of analogs and derivatives of component proteins can be chemically synthesized. For example, a peptide corresponding to a portion of a component protein, which comprises the desired domain or mediates the desired activity in vitro (e.g., complex formation) can be synthesized by use of a peptide synthesizer. Furthermore, if desired, non-classical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the protein sequence.

In cases where natural products are suspected of being mutant or are isolated from new species, the amino acid sequence of a component protein isolated from the natural source, as well as those expressed in vitro, or from synthesized expression vectors in vivo or in vitro, can be determined from analysis of the DNA sequence, or alternatively, by direct sequencing of the isolated protein. Such analysis can be performed by manual sequencing or through use of an automated amino acid sequenator.

The complexes can also be analyzed by hydrophilicity analysis (Hopp and Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828). A hydrophilicity profile can be used to identify the hydrophobic and hydrophilic regions of the proteins, and help predict their orientation in designing substrates for experimental manipulation, such as in binding experiments, antibody synthesis, etc. Secondary structural analysis can also be done to identify regions of the component proteins, or their derivatives, that assume specific structures (Chou and Fasman, 1974, Biochemistry 13:222-23). Manipulation, translation, secondary structure prediction, hydrophilicity and hydrophobicity profile predictions, open reading frame prediction and plotting, and determination of sequence homologies, etc., can be accomplished using computer software programs available in the art.

Other methods of structural analysis including but not limited to X-ray crystallography (Engstrom, 1974, Biochem. Exp. Biol. 11:7-13), mass spectroscopy and gas chromatography (Methods in Protein Science, J. Wiley and Sons, New York, 1997), and computer modeling (Fletterick and Zoller, eds., 1986, Computer Graphics and Molecular Modeling, In: Current Communications in Molecular Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, New York) can also be employed.

#### 4.2 ANTIBODIES TO PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

According to the present invention, a protein complex of the present invention comprising a first protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in fourth column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in fifth column of table 1, or a functionally active fragment or functionally active derivative thereof, can be used as an immunogen to generate antibodies which immunospecifically bind such immunogen. According to the present invention, also a protein complex of the present invention can be used as an immunogen to generate antibodies which immunospecifically bind to such immunogen comprising all proteins listed in fifth column of table 1.

Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library. In a specific embodiment, antibodies to a complex comprising human protein components are produced. In another embodiment, a complex formed from a fragment of said first protein and a fragment of said second protein, which fragments contain the protein domain that interacts with the other member of the complex, are used as an immunogen for antibody production. In a preferred embodiment, the antibody specific for the complex in that the antibody does not bind the individual protein components of the complex.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. Preferred polyclonal antibody compositions are ones that have been selected for antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred polyclonal antibody preparations are ones that contain only antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a polypeptide of the invention. In such a manner, the only human epitope or epitopes recognized by the resulting antibody compositions raised against this immunogen will be present as part of a polypeptide or polypeptides of the invention.

The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA)

using immobilized polypeptide. If desired, the antibody molecules can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. Alternatively, antibodies specific for a protein or polypeptide of the invention can be selected for (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those on the desired protein or polypeptide of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein or polypeptide of the invention.

At an appropriate time after immunization, e.g., when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, 1975, *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al., 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al., 1985, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* 1994, Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage



display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al., 1991, *Bio/Technology* 9:1370-1372; Hay et al., 1992, *Hum. Antibod. Hybridomas* 3:81-85; Huse et al., 1989, *Science* 246:1275-1281; Griffiths et al., 1993, *EMBO J.* 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, e.g., Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al., 1988, *Science* 240:1041-1043; Liu et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al., 1987, *J. Immunol.* 139:3521-3526; Sun et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al., 1987, *Canc. Res.* 47:999-1005; Wood et al., 1985, *Nature* 314:446-449; and Shaw et al., 1988, *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, 1985, *Science* 229:1202-1207; Oi et al., 1986, *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al., 1986, *Nature* 321:552-525; Verhoeyan et al., 1988, *Science* 239:1534; and Beidler et al., 1988, *J. Immunol.* 141:4053-4060.



Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, 1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., 1994, *Bio/technology* 12:899-903).

Antibody fragments that contain the idiotypes of the complex can be generated by techniques known in the art. For example, such fragments include, but are not limited to, the F(ab')<sub>2</sub> fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragment that can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragment; the Fab fragment that can be generated by treating the antibody molecular with papain and a reducing agent; and Fv fragments.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, e.g., ELISA (enzyme-linked immunosorbent assay). To select antibodies specific to a particular domain of the complex, or a derivative thereof, one may assay generated hybridomas for a product that binds to the fragment of the complex, or a derivative thereof, that contains such a

domain. For selection of an antibody that specifically binds a complex of the present, or a derivative, or homologue thereof, but which does not specifically bind to the individual proteins of the complex, or a derivative, or homologue thereof, one can select on the basis of positive binding to the complex and a lack of binding to the individual protein components.

Antibodies specific to a domain of the complex, or a derivative, or homologue thereof, are also provided.

The foregoing antibodies can be used in methods known in the art relating to the localization and/or quantification of the complexes of the invention, e.g., for imaging these proteins, measuring levels thereof in appropriate physiological samples (by immunoassay), in diagnostic methods, etc. This holds true also for a derivative, or homologue thereof of a complex.

In another embodiment of the invention (see *infra*), an antibody to a complex or a fragment of such antibodies containing the antibody binding domain, is a therapeutic.

#### 4.3 DIAGNOSTIC, PROGNOSTIC, AND SCREENING USES OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The particular protein complexes and proteins of the present invention may be markers of normal physiological processes, and thus have diagnostic utility. Further, definition of particular groups of patients with elevations or deficiencies of a protein complex of the present invention, or wherein the protein complex has a change in protein component composition, can lead to new nosological classifications of diseases, furthering diagnostic ability.

Detecting levels of protein complexes, or individual component proteins that form the complexes, or detecting levels of the mRNAs encoding the components of the complex, may be used in diagnosis, prognosis, and/or staging to follow the course of a disease state, to follow a therapeutic response, etc.

A protein complex of the present invention and the individual components of the complex and a derivative, analog or subsequence thereof, encoding nucleic acids (and sequences complementary thereto), and anti-complex antibodies and antibodies directed against individual components that can form the complex, are useful in diagnostics. The foregoing molecules can be used in assays, such as immunoassays, to detect,

prognose, diagnose, or monitor various conditions, diseases, and disorders characterized by aberrant levels of a complex or aberrant component composition of a complex, or monitor the treatment of such various conditions, diseases, and disorders.

In particular, such an immunoassay is carried out by a method comprising contacting a sample derived from a patient with an anti-complex antibody under conditions such that immunospecific binding can occur, and detecting or measuring the amount of any immunospecific binding by the antibody. In a specific aspect, such binding of antibody, in tissue sections, can be used to detect aberrant complex localization, or aberrant (e.g., high, low or absent) levels of a protein complex or complexes. In a specific embodiment, an antibody to the complex can be used to assay a patient tissue or serum sample for the presence of the complex, where an aberrant level of the complex is an indication of a diseased condition. By "aberrant levels" is meant increased or decreased levels relative to that present, or a standard level representing that present, in an analogous sample from a portion or fluid of the body, or from a subject not having the disorder.

The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few known in the art.

Nucleic acids encoding the components of the protein complex and related nucleic acid sequences and subsequences, including complementary sequences, can be used in hybridization assays. The nucleic acid sequences, or subsequences thereof, comprising about at least 8 nucleotides, can be used as hybridization probes. Hybridization assays can be used to detect, prognose, diagnose, or monitor conditions, disorders, or disease states associated with aberrant levels of the mRNAs encoding the components of a complex as described, supra. In particular, such a hybridization assay is carried out by a method comprising contacting a sample containing nucleic acid with a nucleic acid probe capable of hybridizing to component protein coding DNA or RNA, under conditions such that hybridization can occur, and detecting or measuring any resulting hybridization.



In specific embodiments, diseases and disorders involving or characterized by aberrant levels of a protein complex or aberrant complex composition can be diagnosed, or its suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by determining the component protein composition of the complex, or detecting aberrant levels of a member of the complex or un-complexed component proteins or encoding nucleic acids, or functional activity including, but not restricted to, binding to an interacting partner, or by detecting mutations in component protein RNA, DNA or protein (e.g., mutations such as translocations, truncations, changes in nucleotide or amino acid sequence relative to wild-type that cause increased or decreased expression or activity of a complex, and/or component protein).

By way of example, levels of a protein complex and the individual components of a complex can be detected by immunoassay, levels of component protein RNA or DNA can be detected by hybridization assays (e.g., Northern blots, dot blots, RNase protection assays), and binding of component proteins to each other (e.g., complex formation) can be measured by binding assays commonly known in the art. Translocations and point mutations in component protein genes can be detected by Southern blotting, RFLP analysis, PCR using primers that preferably generate a fragment spanning at least most of the gene by sequencing of genomic DNA or cDNA obtained from the patient, etc.

Assays well known in the art (e.g., assays described above such as immunoassays, nucleic acid hybridization assays, activity assays, etc.) can be used to determine whether one or more particular protein complexes are present at either increased or decreased levels, or are absent, in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the levels in samples from subjects not having such a disease or disorder, or having a predisposition to develop such a disease or disorder. Additionally, these assays can be used to determine whether the ratio of the complex to the un-complexed components of the complex, is increased or decreased in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the ratio in samples from subjects not having such a disease or disorder.

In the event that levels of one or more particular protein complexes (i.e., complexes formed from component protein derivatives, homologs, fragments, or analogs) are determined to be increased in patients suffering from a particular disease or



disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder, or predisposition for a disease or disorder, can be diagnosed, have prognosis defined for, be screened for, or be monitored by detecting increased levels of the one or more protein complexes, increased levels of the mRNA that encodes one or more members of the one or more particular protein complexes, or by detecting increased complex functional activity.

Accordingly, in a specific embodiment of the present invention, diseases and disorders involving increased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting increased levels of the one or more protein complexes, the mRNA encoding both members of the complex, or complex functional activity, or by detecting mutations in the component proteins that stabilize or enhance complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that stabilize or enhance complex formation.

In the event that levels of one or more particular protein complexes are determined to be decreased in patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder or predisposition for a disease or disorder can be diagnosed, have its prognosis determined, be screened for, or be monitored by detecting decreased levels of the one or more protein complexes, the mRNA that encodes one or more members of the particular one or more protein complexes, or by detecting decreased protein complex functional activity.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving decreased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting decreased levels of the one or more protein complexes, the mRNA encoding one or more members of the one or more complexes, or complex functional activity, or by detecting mutations in the component proteins that decrease complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that decrease complex formation.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving aberrant compositions of the complexes can be diagnosed, or their suspected

presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting the component proteins of one or more complexes, or the mRNA encoding the members of the one or more complexes.

The use of detection techniques, especially those involving antibodies against a protein complex, provides a method of detecting specific cells that express the complex or component proteins. Using such assays, specific cell types can be defined in which one or more particular protein complexes are expressed, and the presence of the complex or component proteins can be correlated with cell viability, state, health, etc.

Also embodied are methods to detect a protein complex of the present invention in cell culture models that express particular protein complexes or derivatives thereof, for the purpose of characterizing or preparing the complexes for harvest. This embodiment includes cell sorting of prokaryotes such as but not restricted to bacteria (Davey and Kell, 1996, *Microbiol. Rev.* 60:641-696), primary cultures and tissue specimens from eukaryotes, including mammalian species such as human (Steele et al., 1996, *Clin. Obstet. Gynecol* 39:801-813), and continuous cell cultures (Orfao and Ruiz-Arguelles, 1996, *Clin. Biochem.* 29:5-9). Such isolations can be used as methods of diagnosis, described, *supra*.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation.

Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus

have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.

#### 4.4 THERAPEUTIC USES OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The present invention is directed to a method for treatment or prevention of various diseases and disorders by administration of a therapeutic compound (termed herein "therapeutic"). Such "therapeutics" include, but are not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments) of the foregoing (e.g., as described hereinabove); antibodies thereto (as described hereinabove); nucleic acids encoding the component protein, and analogs or derivatives, thereof (e.g., as described hereinabove); component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The protein complexes as identified herein can be implicated in processes which are implicated in or associated with pathological conditions.

These disorders are treated or prevented by administration of a therapeutic that modulates (i.e. inhibits or promotes) protein complex activity or formation or modulates its function or composition. Diseases or disorders associated with aberrant levels of complex activity or formation, or aberrant levels or activity of the component proteins, or aberrant complex composition or a change in the function, may be treated by administration of a therapeutic that modulates complex formation or activity or by the administration of a protein complex.



Therapeutics may also be administered to modulate complex formation or activity or level thereof in a microbial organism such as yeast, fungi such as *Candida albicans* causing an infectious disease in animals or humans.

Diseases and disorders characterized by increased (relative to a subject not suffering from the disease or disorder) complex levels or activity can be treated with therapeutics that antagonize (i.e., reduce or inhibit) complex formation or activity. Therapeutics that can be used include, but are not limited to, the component proteins or an analog, derivative or fragment of the component protein; anti-complex antibodies (e.g., antibodies specific for the protein complex, or a fragment or derivative of the antibody containing the binding region thereof; nucleic acids encoding the component proteins; antisense nucleic acids complementary to nucleic acids encoding the component proteins; and nucleic acids encoding the component protein that are dysfunctional due to, e.g., a heterologous insertion within the protein coding sequence, that are used to "knockout" endogenous protein function by homologous recombination, see, e.g., Capecchi, 1989, *Science* 244:1288-1292. In one embodiment, a therapeutic is 1, 2 or more antisense nucleic acids which are complementary to 1, 2, or more nucleic acids, respectively, that encode component proteins of a complex.

In a specific embodiment of the present invention, a nucleic acid containing a portion of a component protein gene in which gene sequences flank (are both 5' and 3' to) a different gene sequence, is used as a component protein antagonist, or to promote component protein inactivation by homologous recombination (see also, Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342: 435-438). Additionally, mutants or derivatives of a component protein that has greater affinity for another component protein or the complex than wild type may be administered to compete with wild type protein for binding, thereby reducing the levels of complexes containing the wild type protein. Other therapeutics that inhibit complex function can be identified by use of known convenient *in vitro* assays, e.g., based on their ability to inhibit complex formation, or as described in Section 4.5, *infra*.

In specific embodiments, therapeutics that antagonize complex formation or activity are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an increased (relative to normal or desired) level of a complex, for example, in patients where complexes are overactive or overexpressed; or (2) in diseases or disorders where an *in vitro* (or *in vivo*) assay (see *infra*) indicates the utility of antagonist administration. Increased levels of a complex can be readily detected, e.g.,



by quantifying protein and/or RNA, by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, or structure and/or activity of the expressed complex (or the encoding mRNA). Many methods standard in the art can be thus employed including, but not limited to, immunoassays to detect complexes and/or visualize complexes (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.), and/or hybridization assays to detect concurrent expression of component protein mRNA (e.g., Northern assays, dot blot analysis, in situ hybridization, etc.).

A more specific embodiment of the present invention is directed to a method of reducing complex expression (i.e., expression of the protein components of the complex and/or formation of the complex) by targeting mRNAs that express the protein moieties. RNA therapeutics currently fall within three classes, antisense species, ribozymes, or RNA aptamers (Good et al., 1997, *Gene Therapy* 4:45-54).

Antisense oligonucleotides have been the most widely used. By way of example, but not limitation, antisense oligonucleotide methodology to reduce complex formation is presented below, *infra*. Ribozyme therapy involves the administration, induced expression, etc. of small RNA molecules with enzymatic ability to cleave, bind, or otherwise inactivate specific RNAs, to reduce or eliminate expression of particular proteins (Grassi and Marini, 1996, *Annals of Medicine* 28:499-510; Gibson, 1996, *Cancer and Metastasis Reviews* 15:287-299). RNA aptamers are specific RNA ligand proteins, such as for Tat and Rev RNA (Good et al., 1997, *Gene Therapy* 4:45-54) that can specifically inhibit their translation. Aptamers specific for component proteins can be identified by many methods well known in the art, for example, by affecting the formation of a complex in the protein-protein interaction assay described, *infra*.

In another embodiment, the activity or levels of a component protein are reduced by administration of another component protein, or the encoding nucleic acid, or an antibody that immunospecifically binds to the component protein, or a fragment or a derivative of the antibody containing the binding domain thereof.

In another aspect of the invention, diseases or disorders associated with increased levels of an component protein of the complex may be treated or prevented by administration of a therapeutic that increases complex formation if the complex formation acts to reduce or inactivate the component protein through complex formation. Such diseases or disorders can be treated or prevented by administration of one component

member of the complex, administration of antibodies or other molecules that stabilize the complex, etc.

Diseases and disorders associated with underexpression of a complex, or a component protein, are treated or prevented by administration of a therapeutic that promotes (i.e., increases or supplies) complex levels and/or function, or individual component protein function. Examples of such a therapeutic include but are not limited to a complex or a derivative, analog or fragment of the complex that are functionally active (e.g., able to form a complex), un-complexed component proteins and derivatives, analogs, and fragments of un-complexed component proteins, and nucleic acids encoding the members of a complex or functionally active derivatives or fragments of the members of the complex, e.g., for use in gene therapy. In a specific embodiment, a therapeutic includes derivatives, homologs or fragments of a component protein that increase and/or stabilize complex formation. Examples of other agonists can be identified using in vitro assays or animal models, examples of which are described, *infra*.

In yet other specific embodiments of the present invention, therapeutics that promote complex function are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an absence or decreased (relative to normal or desired) level of a complex, for example, in patients where a complex, or the individual components necessary to form the complex, is lacking, genetically defective, biologically inactive or underactive, or under-expressed; or (2) in diseases or disorders wherein an in vitro or in vivo assay (see, *infra*) indicates the utility of complex agonist administration. The absence or decreased level of a complex, component protein or function can be readily detected, e.g., by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, structure and/or activity of the expressed complex and/or the concurrent expression of mRNA encoding the two components of the complex. Many methods standard in the art can be thus employed, including but not limited to immunoassays to detect and/or visualize a complex, or the individual components of a complex (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs encoding the individual protein components of a complex by detecting and/or visualizing component mRNA concurrently or separately using, e.g., Northern assays, dot blot analysis, in situ hybridization, etc.

In specific embodiments, the activity or levels of a component protein are increased by administration of another component protein of the same complex, or a derivative, homolog or analog thereof, a nucleic acid encoding the other component, or an agent that stabilizes or enhances the other component, or a fragment or derivative of such an agent.

Generally, administration of products of species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, a human complex, or derivative, homolog or analog thereof; nucleic acids encoding the members of the human complex or a derivative, homolog or analog thereof; an antibody to a human complex, or a derivative thereof; or other human agents that affect component proteins or the complex, are therapeutically or prophylactically administered to a human patient.

Preferably, suitable in vitro or in vivo assays are utilized to determine the effect of a specific therapeutic and whether its administration is indicated for treatment of the affected tissue or individual.

In various specific embodiments, in vitro assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if a therapeutic has a desired effect upon such cell types.

Compounds for use in therapy can be tested in suitable animal model systems prior to testing in humans, including, but not limited to, rats, mice, chicken, cows, monkeys, rabbits, etc. For in vivo testing, prior to administration to humans, any animal model system known in the art may be used. Additional descriptions and sources of therapeutics that can be used according to the invention are found in Sections 4.1 to 4.3 and 4.7 herein.

#### 4.4.1 GENE THERAPY

In a specific embodiment of the present invention, nucleic acids comprising a sequence encoding the component proteins, or a functional derivative thereof, are administered to modulate complex activity or formation by way of gene therapy. Gene therapy refers to therapy performed by the administration of a nucleic acid to a subject. In this embodiment of the present invention, the nucleic acid expresses its encoded protein(s) that mediates a therapeutic effect by modulating complex activity or formation.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., 1993, *Clinical Pharmacy* 12:488-505; Wu and Wu, 1991, *Biotherapy* 3:87-95; Tolstoshev, 1993, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596; Mulligan, 1993, *Science* 260:926-932; Morgan and Anderson, 1993, *Ann. Rev. Biochem.* 62:191-217; and May, 1993, *TIBTECH* 11:155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al., eds., 1993, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY; and Kriegler, 1990, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY.

In a preferred aspect, the therapeutic comprises a nucleic acid that is part of an expression vector that expresses one or more of the component proteins, or fragments or chimeric proteins thereof, in a suitable host. In particular, such a nucleic acid has a promoter operably linked to the protein coding region(s) (or, less preferably separate promoters linked to the separate coding regions separately), said promoter being inducible or constitutive, and optionally, tissue-specific. In another particular embodiment, a nucleic acid molecule is used in which the coding sequences, and any other desired sequences, are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intra-chromosomal expression of the component protein nucleic acids (Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342:435-438).

Delivery of the nucleic acid into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vector, or indirect, in which case, cells are first transformed with the nucleic acid in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

In a specific embodiment, the nucleic acid is directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by infection using a defective or attenuated retroviral or other viral vector (U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors, or through use of transfecting agents, by encapsulation in liposomes,



microparticles, or microcapsules, or by administering it in linkage to a peptide that is known to enter the nucleus, or by administering it in linkage to a ligand subject to receptor-mediated endocytosis that can be used to target cell types specifically expressing the receptors (e.g., Wu and Wu, 1987, *J. Biol. Chem.* 262:4429-4432), etc. In another embodiment, a nucleic acid-ligand complex can be formed in which the ligand comprises a fusogenic viral peptide that disrupts endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., International Patent Publications WO 92/06180; WO 92/22635; WO 92/20316; WO 93/14188; and WO 93/20221. Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342:435-438).

In a specific embodiment, a viral vector that contains the component protein encoding nucleic acids is used. For example, a retroviral vector can be used (Miller et al., 1993, *Meth. Enzymol.* 217:581-599). These retroviral vectors have been modified to delete retroviral sequences that are not necessary for packaging of the viral genome and integration into host cell DNA. The encoding nucleic acids to be used in gene therapy is/are cloned into the vector, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., 1994, *Biotherapy* 6:291-302, which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are Clowes et al., 1994, *J. Clin. Invest.* 93:644-651; Kiem et al., 1994, *Blood* 83:1467-1473; Salmons and Gunzberg, 1993, *Human Gene Therapy* 4:129-141; and Grossman and Wilson, 1993, *Curr. Opin. in Genetics and Devel.* 3:110-114.

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are the liver, the central nervous system, endothelial cells and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, 1993, *Curr. Opin. Genet. Devel.* 3:499-503, discuss adenovirus-based gene therapy. The use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys has

been demonstrated by Bout et al., 1994, Human Gene Therapy 5:3-10. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., 1991, Science 252:431-434; Rosenfeld et al., 1992, Cell 68:143-155; and Mastrangeli et al., 1993, J. Clin. Invest. 91:225-234.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., 1993, Proc. Soc. Exp. Biol. Med. 204:289-300).

Another approach to gene therapy involves transferring a gene into cells in tissue culture by methods such as electroporation, lipofection, calcium phosphate-mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene from those that have not. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art including, but not limited to, transfection by electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, 1993, Meth. Enzymol. 217:599-618; Cohen et al., 1993, Meth. Enzymol. 217:618-644; Cline, 1985, Pharmac. Ther. 29:69-92) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably, is heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. In a preferred embodiment, epithelial cells are injected, e.g., subcutaneously. In another embodiment, recombinant skin cells may be applied as a skin graft onto the patient. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial

cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes, blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, and granulocytes, various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, a component protein encoding nucleic acid is/are introduced into the cells such that the gene or genes are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention. Such stem cells include but are not limited to hematopoietic stem cells (HSCs), stem cells of epithelial tissues such as the skin and the lining of the gut, embryonic heart muscle cells, liver stem cells (International Patent Publication WO 94/08598), and neural stem cells (Stemple and Anderson, 1992, Cell 71:973-985).

Epithelial stem cells (ESCs), or keratinocytes, can be obtained from tissues such as the skin and the lining of the gut by known procedures (Rheinwald, 1980, Meth. Cell Biol. 2A:229). In stratified epithelial tissue such as the skin, renewal occurs by mitosis of stem cells within the germinal layer, the layer closest to the basal lamina. Similarly, stem cells within the lining of the gut provide for a rapid renewal rate of this tissue. ESCs or keratinocytes obtained from the skin or lining of the gut of a patient or donor can be grown in tissue culture (Rheinwald, 1980, Meth. Cell Bio. 2A:229; Pittelkow and Scott, 1986, Mayo Clinic Proc. 61:771). If the ESCs are provided by a donor, a method for suppression of host versus graft reactivity (e.g., irradiation, or drug or antibody administration to promote moderate immunosuppression) can also be used.

With respect to hematopoietic stem cells (HSCs), any technique that provides for the isolation, propagation, and maintenance in vitro of HSCs can be used in this embodiment of the invention. Techniques by which this may be accomplished include (a) the isolation and establishment of HSC cultures from bone marrow cells isolated from the future host, or a donor, or (b) the use of previously established long-term HSC cultures, which may be allogeneic or xenogeneic. Non-autologous HSCs are used preferably in conjunction with a method of suppressing transplantation immune reactions



between the future host and patient. In a particular embodiment of the present invention, human bone marrow cells can be obtained from the posterior iliac crest by needle aspiration (see, e.g., Kodo et al., 1984, J. Clin. Invest. 73: 1377-1384). In a preferred embodiment of the present invention, the HSCs can be made highly enriched or in substantially pure form. This enrichment can be accomplished before, during, or after long-term culturing, and can be done by any technique known in the art. Long-term cultures of bone marrow cells can be established and maintained by using, for example, modified Dexter cell culture techniques (Dexter et al., 1977, J. Cell Physiol. 91:335) or Witlock-Witte culture techniques (Witlock and Witte, 1982, Proc. Natl. Acad. Sci. USA 79:3608-3612).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Additional methods can be adapted for use to deliver a nucleic acid encoding the component proteins, or functional derivatives thereof, e.g., as described in Section 4.1, *supra*.

#### 4.4.2 USE OF ANTISENSE OLIGONUCLEOTIDES FOR SUPPRESSION OF PROTEIN COMPLEX FORMATION OR PROTEIN COMPLEX/PROTEIN ACTIVITY

In a specific embodiment of the present invention, protein complex activity and formation and protein activity is inhibited by use of antisense nucleic acids for the component proteins of the complex, that inhibit transcription and/or translation of their complementary sequence. The present invention provides the therapeutic or prophylactic use of nucleic acids of at least six nucleotides that are antisense to a gene or cDNA encoding a component protein, or a portion thereof. An "antisense" nucleic acid as used herein refers to a nucleic acid capable of hybridizing to a sequence-specific portion of a component protein RNA (preferably mRNA) by virtue of some sequence complementarity. The antisense nucleic acid may be complementary to a coding and/or noncoding region of a component protein mRNA. Such antisense nucleic acids that inhibit complex formation or activity have utility as therapeutics, and can be used in the treatment or prevention of disorders as described *supra*.



The antisense nucleic acids of the invention can be oligonucleotides that are double-stranded or single-stranded, RNA or DNA, or a modification or derivative thereof, which can be directly administered to a cell, or which can be produced intracellularly by transcription of exogenous, introduced sequences.

In another embodiment, the present invention is directed to a method for inhibiting the expression of component protein nucleic acid sequences, in a prokaryotic or eukaryotic cell, comprising providing the cell with an effective amount of a composition comprising an antisense nucleic acid of the component protein, or a derivative thereof, of the invention.

The antisense nucleic acids are of at least six nucleotides and are preferably oligonucleotides, ranging from 6 to about 200 nucleotides. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 15 nucleotides, at least 100 nucleotides, or at least 200 nucleotides. The oligonucleotides can be DNA or RNA or chimeric mixtures, or derivatives or modified versions thereof, and either single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. USA 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648-652; International Patent Publication No. WO 88/09810) or blood-brain barrier (see, e.g., International Patent Publication No. WO 89/10134), hybridization-triggered cleavage agents (see, e.g., Krol et al., 1988, BioTechniques 6:958-976), or intercalating agents (see, e.g., Zon, 1988, Pharm. Res. 5:539-549).

In a preferred aspect of the invention, an antisense oligonucleotide is provided, preferably as single-stranded DNA. The oligonucleotide may be modified at any position in its structure with constituents generally known in the art.

The antisense oligonucleotides may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thio-uridine, 5-carboxymethylaminomethyluracil, dihydrouracil,  $\beta$ -D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil,

$\beta$ -D-mannosylqueosine, 5N-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

In another embodiment, the oligonucleotide comprises at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal, or an analog of the foregoing.

In yet another embodiment, the oligonucleotide is a 2'-a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641).

The oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization-triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

Oligonucleotides of the invention may be synthesized by standard methods known in the art, e.g., by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligo-nucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. USA 85:7448-7451), etc.

In a specific embodiment, the antisense oligonucleotides comprise catalytic RNAs, or ribozymes (see, e.g., International Patent Publication No. WO 90/11364; Sarver et al., 1990, Science 247:1222-1225). In another embodiment, the oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analog (Inoue et al., 1987, FEBS Lett. 215:327-330).

In an alternative embodiment, the antisense nucleic acids of the invention are produced intracellularly by transcription from an exogenous sequence. For example, a vector can be introduced in vivo such that it is taken up by a cell, within which cell the vector or a portion thereof is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the component protein. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art to be capable of replication and expression in mammalian cells. Expression of the sequences encoding the antisense RNAs can be by any promoter known in the art to act in mammalian, preferably human, cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, 1981, *Nature* 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., 1980, *Cell* 22:787-797), the herpes thymidine kinase promoter (Wagner et al., 1981, *Proc. Natl. Acad. Sci. USA* 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster et al., 1982, *Nature* 296:39-42), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a component protein gene, preferably a human gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with a component protein RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

The component protein antisense nucleic acids can be used to treat (or prevent) disorders of a cell type that expresses, or preferably overexpresses, a protein complex.

Cell types that express or overexpress component protein RNA can be identified by various methods known in the art. Such methods include, but are not limited to,

hybridization with component protein-specific nucleic acids (e.g., by Northern blot hybridization, dot blot hybridization, or in situ hybridization), or by observing the ability of RNA from the cell type to be translated in vitro into the component protein by immunohistochemistry, Western blot analysis, ELISA, etc. In a preferred aspect, primary tissue from a patient can be assayed for protein expression prior to treatment, e.g., by immunocytochemistry, in situ hybridization, or any number of methods to detect protein or mRNA expression.

Pharmaceutical compositions of the invention (see Section 4.7, *infra*), comprising an effective amount of a protein component antisense nucleic acid in a pharmaceutically acceptable carrier can be administered to a patient having a disease or disorder that is of a type that expresses or overexpresses a protein complex of the present invention.

The amount of antisense nucleic acid that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. Where possible, it is desirable to determine the antisense cytotoxicity in vitro, and then in useful animal model systems, prior to testing and use in humans.

In a specific embodiment, pharmaceutical compositions comprising antisense nucleic acids are administered via liposomes, microparticles, or microcapsules. In various embodiments of the invention, it may be useful to use such compositions to achieve sustained release of the antisense nucleic acids. In a specific embodiment, it may be desirable to utilize liposomes targeted via antibodies to specific identifiable central nervous system cell types (Leonetti et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2448-2451; Renneisen et al., 1990, J. Biol. Chem. 265:16337-16342).

#### 4.5 ASSAYS OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION AND DERIVATIVES AND ANALOGS THEREOF

The functional activity of a protein complex of the present invention, or a derivative, fragment or analog thereof or protein component thereof, can be assayed by various methods. Potential modulators (e.g., agonists and antagonists) of complex activity or formation, e.g., anti-complex antibodies and antisense nucleic acids, can be assayed for the ability to modulate complex activity or formation.



In one embodiment of the present invention, where one is assaying for the ability to bind or compete with a wild-type complex for binding to an anti-complex antibody, various immunoassays known in the art can be used, including but not limited to competitive and non-competitive assay systems using techniques such as radioimmunoassay, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitin reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels), western blot analysis, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

The expression of the component protein genes (both endogenous and those expressed from cloned DNA containing the genes) can be detected using techniques known in the art, including but not limited to Southern hybridization (Southern, 1975, J. Mol. Biol. 98:503-517), northern hybridization (see, e.g., Freeman et al., 1982, Proc. Natl. Acad. Sci. USA 80:4094-4098), restriction endonuclease mapping (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, 2<sup>nd</sup> Ed. Cold Spring Harbor Laboratory Press, New York), RNase protection assays (Current Protocols in Molecular Biology, John Wiley and Sons, New York, 1997), DNA sequence analysis, and polymerase chain reaction amplification (PCR; U.S. Patent Nos. 4,683,202, 4,683,195, and 4,889,818; Gyllenstein et al., 1988, Proc. Natl. Acad. Sci. USA 85:7652-7657; Ochman et al., 1988, Genetics 120:621-623; Loh et al., 1989, Science 243:217-220) followed by Southern hybridization with probes specific for the component protein genes, in various cell types. Methods of amplification other than PCR commonly known in the art can be employed. In one embodiment, Southern hybridization can be used to detect genetic linkage of component protein gene mutations to physiological or pathological states. Various cell types, at various stages of development, can be characterized for their expression of component proteins at the same time and in the same cells. The stringency of the hybridization conditions for northern or Southern blot analysis can be manipulated to ensure detection of nucleic acids with the desired degree of relatedness to the specific

probes used. Modifications to these methods and other methods commonly known in the art can be used.

Derivatives (e.g., fragments), homologs and analogs of one component protein can be assayed for binding to another component protein in the same complex by any method known in the art, for example the modified yeast matrix mating test described in Section 4.6.1 *infra*, immunoprecipitation with an antibody that binds to the component protein complexed with other component proteins in the same complex, followed by size fractionation of the immunoprecipitated proteins (e.g., by denaturing or nondenaturing polyacrylamide gel electrophoresis), Western blot analysis, etc.

One embodiment of the invention provides a method for screening a derivative, homolog or analog of a component protein for biological activity comprising contacting said derivative, homolog or analog of the component protein with the other component proteins in the same complex; and detecting the formation of a complex between said derivative, homolog or analog of the component protein and the other component proteins; wherein detecting formation of said complex indicates that said derivative, homolog or analog of has biological (e.g., binding) activity.

The invention also provides methods of modulating the activity of a component protein that can participate in a protein complex by administration of a binding partner of that protein or derivative, homolog or analog thereof.

In a specific embodiment of the present invention, a protein complex of the present invention is administered to treat or prevent a disease or disorder, since the complex and/or component proteins have been implicated in the disease and disorder. Accordingly, a protein complex or a derivative, homolog, analog or fragment thereof, nucleic acids encoding the component proteins, anti-complex antibodies, and other modulators of protein complex activity, can be tested for activity in treating or preventing a disease or disorder in *in vitro* and *in vivo* assays.

In one embodiment, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by contacting cultured cells that exhibit an indicator of the disease *in vitro*, with the therapeutic, and comparing the level of said indicator in the cells contacted with the therapeutic, with said level of said indicator in cells not so contacted, wherein a lower level in said contacted cells indicates that the therapeutic has activity in treating or preventing the disease.

In another embodiment of the invention, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by administering the therapeutic to

a test animal that is predisposed to develop symptoms of a disease, and measuring the change in said symptoms of the disease after administration of said therapeutic, wherein a reduction in the severity of the symptoms of the disease or prevention of the symptoms of the disease indicates that the therapeutic has activity in treating or preventing the disease. Such a test animal can be any one of a number of animal models known in the art for disease. These animal models are well known in the art. These animal models include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention.

#### 4.6 SCREENING FOR MODULATORS OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

A complex of the present invention, the component proteins of the complex and nucleic acids encoding the component proteins, as well as derivatives and fragments of the amino and nucleic acids, can be used to screen for compounds that bind to, or modulate the amount of, activity of, or protein component composition of, said complex, and thus, have potential use as modulators, i.e., agonists or antagonists, of complex activity, and/or complex formation, i.e., the amount of complex formed, and/or protein component composition of the complex.

Thus, the present invention is also directed to methods for screening for molecules that bind to, or modulate the function of, amount of, activity of, formation of or protein component composition of, a complex of the present invention. In one embodiment of the invention, the method for screening for a molecule that modulates directly or indirectly the function, activity or formation of a complex of the present invention comprises exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules under conditions conducive to modulation; and determining the amount of, the biochemical activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependend on the complex and/or the abundance and/or activity of a protein or protein complex dependend on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular



localization and/or a change in the transcription level of a gene depend on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation.

Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.

In another embodiment, the present invention further relates to a process for the identification and/or preparation of an effector of the complex comprising the step of



bringing into contact a product of any of claims 1 to 8 with a compound, a mixture or a library of compounds and determining whether the compound or a certain compound of the mixture or library binds to the product and/or effects the products biological activity and optionally further purifying the compound positively tested as effector.

In another embodiment, the present invention is directed to a method for screening for a molecule that binds a protein complex of the present invention comprising exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules; and determining whether said complex is bound by any of said candidate molecules. Such screening assays can be carried out using cell-free and cell-based methods that are commonly known in the art in vitro, in vivo or ex vivo. For example, an isolated complex can be employed, or a cell can be contacted with the candidate molecule and the complex can be isolated from such contacted cells and the isolated complex can be assayed for activity or component composition. In another example, a cell containing the complex can be contacted with the candidate molecule and the levels of the complex in the contacted cell can be measured. Additionally, such assays can be carried out in cells recombinantly expressing a component protein from the fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, and a component protein from fifth column of table 1, or a functionally active fragment or functionally active derivative thereof. Additionally, such assays can also be carried out in cells recombinantly expressing all component proteins from the group of proteins in the fifth column of table 1.

For example, assays can be carried out using recombinant cells expressing the protein components of a complex, to screen for molecules that bind to, or interfere with, or promote complex activity or formation. In preferred embodiments, polypeptide derivatives that have superior stabilities but retain the ability to form a complex (e.g., one or more component proteins modified to be resistant to proteolytic degradation in the binding assay buffers, or to be resistant to oxidative degradation), are used to screen for modulators of complex activity or formation. Such resistant molecules can be generated, e.g., by substitution of amino acids at proteolytic cleavage sites, the use of chemically derivatized amino acids at proteolytic susceptible sites, and the replacement of amino acid residues subject to oxidation, i.e. methionine and cysteine.

A particular aspect of the present invention relates to identifying molecules that inhibit or promote formation or degradation of a complex of the present invention, e.g.,

using the method described for isolating the complex and identifying members of the complex using the TAP assay described in Section 4, *infra*, and in WO 00/09716 and Rigaut et al., 1999, *Nature Biotechnol.* 17:1030-1032, which are each incorporated by reference in their entirety. TNRF1

In another embodiment of the invention, a modulator is identified by administering a candidate molecule to a transgenic non-human animal expressing the complex component proteins from promoters that are not the native promoters of the respective proteins, more preferably where the candidate molecule is also recombinantly expressed in the transgenic non-human animal. Alternatively, the method for identifying such a modulator can be carried out *in vitro*, preferably with a purified complex, and a purified candidate molecule.

Agents/molecules (candidate molecules) to be screened can be provided as mixtures of a limited number of specified compounds, or as compound libraries, peptide libraries and the like. Agents/molecules to be screened may also include all forms of antisera, antisense nucleic acids, etc., that can modulate complex activity or formation. Exemplary candidate molecules and libraries for screening are set forth in Section 4.6.1, *infra*.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and International Patent Publication No. WO 94/18318.

In a specific embodiment, screening can be carried out by contacting the library members with a complex immobilized on a solid phase, and harvesting those library members that bind to the protein (or encoding nucleic acid or derivative). Examples of such screening methods, termed "panning" techniques, are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques* 13:422-427; International Patent Publication No. WO 94/18318; and in references cited hereinabove.

In a specific embodiment, fragments and/or analogs of protein components of a complex, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex formation (amount of complex or composition of complex) or activity in the cell, which thereby inhibit complex activity or formation in the cell.

In one embodiment, agents that modulate (i.e., antagonize or agonize) complex activity or formation can be screened for using a binding inhibition assay, wherein agents are screened for their ability to modulate formation of a complex under aqueous, or physiological, binding conditions in which complex formation occurs in the absence of the agent to be tested. Agents that interfere with the formation of complexes of the invention are identified as antagonists of complex formation. Agents that promote the formation of complexes are identified as agonists of complex formation. Agents that completely block the formation of complexes are identified as inhibitors of complex formation.

Methods for screening may involve labeling the component proteins of the complex with radioligands (e.g.,  $^{125}\text{I}$  or  $^3\text{H}$ ), magnetic ligands (e.g., paramagnetic beads covalently attached to photobiotin acetate), fluorescent ligands (e.g., fluorescein or rhodamine), or enzyme ligands (e.g., luciferase or  $\beta$ -galactosidase). The reactants that bind in solution can then be isolated by one of many techniques known in the art, including but not restricted to, co-immunoprecipitation of the labeled complex moiety using antisera against the unlabeled binding partner (or labeled binding partner with a distinguishable marker from that used on the second labeled complex moiety), immunoaffinity chromatography, size exclusion chromatography, and gradient density centrifugation. In a preferred embodiment, the labeled binding partner is a small fragment or peptidomimetic that is not retained by a commercially available filter. Upon binding, the labeled species is then unable to pass through the filter, providing for a simple assay of complex formation.

Methods commonly known in the art are used to label at least one of the component members of the complex. Suitable labeling methods include, but are not limited to, radiolabeling by incorporation of radiolabeled amino acids, e.g.,  $^3\text{H}$ -leucine or  $^{35}\text{S}$ -methionine, radiolabeling by post-translational iodination with  $^{125}\text{I}$  or  $^{131}\text{I}$  using the chloramine T method, Bolton-Hunter reagents, etc., or labeling with  $^{32}\text{P}$  using phosphorylase and inorganic radiolabeled phosphorous, biotin labeling with photobiotin-acetate and sunlamp exposure, etc. In cases where one of the members of the complex is immobilized, e.g., as described *infra*, the free species is labeled. Where neither of the



interacting species is immobilized, each can be labeled with a distinguishable marker such that isolation of both moieties can be followed to provide for more accurate quantification, and to distinguish the formation of homomeric from heteromeric complexes. Methods that utilize accessory proteins that bind to one of the modified interactants to improve the sensitivity of detection, increase the stability of the complex, etc., are provided.

Typical binding conditions are, for example, but not by way of limitation, in an aqueous salt solution of 10-250 mM NaCl, 5-50 mM Tris-HCl, pH 5-8, and 0.5% Triton X-100 or other detergent that improves specificity of interaction. Metal chelators and/or divalent cations may be added to improve binding and/or reduce proteolysis. Reaction temperatures may include 4, 10, 15, 22, 25, 35, or 42 degrees Celsius, and time of incubation is typically at least 15 seconds, but longer times are preferred to allow binding equilibrium to occur. Particular complexes can be assayed using routine protein binding assays to determine optimal binding conditions for reproducible binding.

The physical parameters of complex formation can be analyzed by quantification of complex formation using assay methods specific for the label used, e.g., liquid scintillation counting for radioactivity detection, enzyme activity for enzyme-labeled moieties, etc. The reaction results are then analyzed utilizing Scatchard analysis, Hill analysis, and other methods commonly known in the arts (see, e.g., *Proteins, Structures, and Molecular Principles*, 2<sup>nd</sup> Edition (1993) Creighton, Ed., W.H. Freeman and Company, New York).

In a second common approach to binding assays, one of the binding species is immobilized on a filter, in a microtiter plate well, in a test tube, to a chromatography matrix, etc., either covalently or non-covalently. Proteins can be covalently immobilized using any method well known in the art, for example, but not limited to the method of Kadonaga and Tjian, 1986, *Proc. Natl. Acad. Sci. USA* 83:5889-5893, i.e., linkage to a cyanogen-bromide derivatized substrate such as CNBr-Sepharose 4B (Pharmacia). Where needed, the use of spacers can reduce steric hindrance by the substrate. Non-covalent attachment of proteins to a substrate include, but are not limited to, attachment of a protein to a charged surface, binding with specific antibodies, binding to a third unrelated interacting protein, etc.

Assays of agents (including cell extracts or a library pool) for competition for binding of one member of a complex (or derivatives thereof) with another member of the



complex labeled by any means (e.g., those means described above) are provided to screen for competitors or enhancers of complex formation.

In specific embodiments, blocking agents to inhibit non-specific binding of reagents to other protein components, or absorptive losses of reagents to plastics, immobilization matrices, etc., are included in the assay mixture. Blocking agents include, but are not restricted to bovine serum albumin,  $\beta$ -casein, nonfat dried milk, Denhardt's reagent, Ficoll, polyvinylpyrrolidone, nonionic detergents (NP40, Triton X-100, Tween 20, Tween 80, etc.), ionic detergents (e.g., SDS, LDS, etc.), polyethylene glycol, etc. Appropriate blocking agent concentrations allow complex formation.

After binding is performed, unbound, labeled protein is removed in the supernatant, and the immobilized protein retaining any bound, labeled protein is washed extensively. The amount of bound label is then quantified using standard methods in the art to detect the label as described, *supra*.

In another specific embodiment screening for modulators of the protein complexes/protein as provided herein can be carried out by attaching those and/or the antibodies as provided herein to a solid carrier. In a further specific embodiment, the invention relates to an array of said molecules.

The preparation of such an array containing different types of proteins, including antibodies) is well known in the art and is apparent to a person skilled in the art (see e.g. Ekins et al., 1989, *J. Pharm. Biomed. Anal.* 7:155-168; Mitchell et al. 2002, *Nature Biotechnol.* 20:225-229; Petricoin et al., 2002, *Lancet* 359:572-577; Templin et al., 2001, *Trends Biotechnol.* 20:160-166; Wilson and Nock, 2001, *Curr. Opin. Chem. Biol.* 6:81-85; Lee et al., 2002 *Science* 295:1702-1705; MacBeath and Schreiber, 2000, *Science* 289:1760; Blawas and Reichert, 1998, *Biomaterials* 19:595; Kane et al., 1999, *Biomaterials* 20:2363; Chen et al., 1997, *Science* 276:1425; Vaugham et al., 1996, *Nature Biotechnol.* 14:309-314; Mahler et al., 1997, *Immunotechnology* 3:31-43; Roberts et al., 1999, *Curr. Opin. Chem. Biol.* 3:268-273; Nord et al., 1997, *Nature Biotechnol.* 15:772-777; Nord et al., 2001, *Eur. J. Biochem.* 268:4269-4277; Brody and Gold, 2000, *Rev. Mol. Biotechnol.* 74:5-13; Karlstroem and Nygren, 2001, *Anal. Biochem.* 295:22-30; Nelson et al., 2000, *Electrophoresis* 21:1155-1163; Honore et al., 2001, *Expert Rev. Mol. Diagn.* 3:265-274; Albala, 2001, *Expert Rev. Mol. Diagn.* 2:145-152, Figeys and Pinto, 2001, *Electrophoresis* 2:208-216 and references in the publications listed here).

Complexes can be attached to an array by different means as will be apparent to a person skilled in the art. Complexes can for example be added to the array via a TAP-

tag (as described in WO/0009716 and in Rigaut et al., 1999, Nature Biotechnol. 10:1030-1032) after the purification step or by another suitable purification scheme as will be apparent to a person skilled in the art.

Optionally, the proteins of the complex can be cross-linked to enhance the stability of the complex. Different methods to cross-link proteins are well known in the art. Reactive end-groups of cross-linking agents include but are not limited to -COOH, -SH, -NH<sub>2</sub> or N-oxy-succinamate.

The spacer of the cross-linking agent should be chosen with respect to the size of the complex to be cross-linked. For small protein complexes, comprising only a few proteins, relatively short spacers are preferable in order to reduce the likelihood of cross-linking separate complexes in the reaction mixture. For larger protein complexes, additional use of larger spacers is preferable in order to facilitate cross-linking between proteins within the complex.

It is preferable to check the success-rate of cross-linking before linking the complex to the carrier.

As will be apparent to a person skilled in the art, the optimal rate of cross-linking need to be determined on a case by case basis. This can be achieved by methods well known in the art, some of which are exemplary described below.

A sufficient rate of cross-linking can be checked f.e. by analysing the cross-linked complex vs. a non-cross-linked complex on a denaturing protein gel.

If cross-linking has been performed successfully, the proteins of the complex are expected to be found in the same lane, whereas the proteins of the non-cross-linked complex are expected to be separated according to their individual characteristics. Optionally the presence of all proteins of the complex can be further checked by peptide-sequencing of proteins in the respective bands using methods well known in the art such as mass spectrometry and/or Edman degradation.

In addition, a rate of crosslinking which is too high should also be avoided. If cross-linking has been carried out too extensively, there will be an increasing amount of cross-linking of the individual protein complex, which potentially interferes with a screening for potential binding partners and/or modulators etc. using the arrays.

The presence of such structures can be determined by methods well known in the art and include e.g. gel-filtration experiments comparing the gel filtration profile solutions containing cross-linked complexes vs. uncross-linked complexes.

Optionally, functional assays as will be apparent to a person skilled in the art, some of which are exemplarily provided herein, can be performed to check the integrity of the complex.

Alternatively, members of the protein complex can be expressed as a single fusion protein and coupled to the matrix as will be apparent to a person skilled in the art.

Optionally, the attachment of the complex or proteins or antibody as outlined above can be further monitored by various methods apparent to a person skilled in the art. Those include, but are not limited to surface plasmon resonance (see e.g. McDonnel, 2001, *Curr. Opin. Chem. Biol.* 5:572-577; Lee, 2001, *Trends Biotechnol.* 19:217-222; Weinberger et al., 2000, 1:395-416; Pearson et al., 2000, *Ann. Clin. Biochem.* 37:119-145; Vely et al., 2000, *Methods Mol. Biol.* 121:313-321; Slepak, 2000, *J. Mol. Recognit.* 13:20-26).

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastrin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKR1-complex, PTK7-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the gamma-secretase activity in vitro of the Presenilin 1 complex include but are not limited to those described in Li Y M et al., 2000, *Proc Natl Acad Sci U S A*, 97:6138-43 and Pinnix I et al., 2001, *J Biol Chem*, 276:481-7.

Exemplary assays useful for measuring the gamma-secretase dependent transcriptional activity of the Presenilin 1 complex include but are not limited to those described in Karlstrom H et al., 2002, *J Biol Chem*, 277:6763-6.

Exemplary assays useful for measuring the formation of amyloid-beta peptides and their aggregated forms of the Presenilin 1 complex include but are not limited to those described in De Strooper B et al., 1998, *Nature*, 391:387-90.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastrin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex, include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastrin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex, include but are not limited to those described in Tian G et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastrin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex, include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the phosphorylation of Tau proteins in vitro or in cells (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of



the Tau complex include but are not limited to those described in Drewes G et al., 1997, *Cell*, 89:297-308.

Exemplary assays useful for measuring the aggregation of Tau proteins into filaments or tangles in vitro or in cells (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Tau complex include but are not limited to those described in Barghorn S et al., 2000, *Biochemistry*, 39:11714-21.

Exemplary assays useful for measuring the transactivation of reporter genes by APP-Gal4/VP16 (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11beta complex include but are not limited to those described in Biederer T et al., 2002, *J Neurosci*, 22:7340-51.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Fe65-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring the transactivation of reporter genes by APP-Gal4/VP16 (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Biederer Thomas et al., 2002, J Neurosci, 22:7340-51.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PSEN2 -complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PSEN2 -complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting of the PSEN2 -complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PSEN2 -complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Nicastrin-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Nicastrin-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Nicastrin-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Nicastrin-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Aph-1a-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Aph-1a-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Aph-1a-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Aph-1a-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pen-2-complex include but are not limited to those described in Vassar R et al., 1999, *Science*, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pen-2-complex include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Pen-2-complex include but are not limited to those described in Tian Gaochao et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pen-2-complex include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.



Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C99 -complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C99 -complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the APP-C99 -complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C99 -complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the DAB1-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the DAB1-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting of the DAB1-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the DAB1-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the JIP1-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting

proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Fe65L2-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Neurotrypsin-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Telencephalin-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.



Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the BACE1 (new)-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the BACE2-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-



C59-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring transcriptional activity in vivo of the Tip60-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring Apoptotic activity of the Tip60-complex include but are not limited to those described in Kinoshita Ayae et al., 2002, J Biol Chem, 277:28530-6.

#### 4.6.1 CANDIDATE MOLECULES

Any molecule known in the art can be tested for its ability to modulate (increase or decrease) the amount of, activity of, or protein component composition of a complex of the present invention as detected by a change in the amount of, activity of, or protein component composition of, said complex. By way of example, a change in the amount of the complex can be detected by detecting a change in the amount of the complex that can be isolated from a cell expressing the complex machinery. For identifying a molecule that modulates complex activity, candidate molecules can be directly provided to a cell expressing the complex machinery, or, in the case of candidate proteins, can be provided by providing their encoding nucleic acids under conditions in which the nucleic acids are recombinantly expressed to produce the candidate proteins within the cell expressing the complex machinery, the complex is then isolated from the cell and the isolated complex is assayed for activity using methods well known in the art, not limited to those described, supra.

This embodiment of the invention is well suited to screen chemical libraries for molecules which modulate, e.g., inhibit, antagonize, or agonize, the amount of, activity of, or protein component composition of the complex. The chemical libraries can be peptide libraries, peptidomimetic libraries, chemically synthesized libraries, recombinant, e.g., phage display libraries, and in vitro translation-based libraries, other non-peptide synthetic organic libraries, etc.

Exemplary libraries are commercially available from several sources (ArQule, Tripos/PanLabs, ChemDesign, Pharmacopoeia). In some cases, these chemical libraries are generated using combinatorial strategies that encode the identity of each

member of the library on a substrate to which the member compound is attached, thus allowing direct and immediate identification of a molecule that is an effective modulator. Thus, in many combinatorial approaches, the position on a plate of a compound specifies that compound's composition. Also, in one example, a single plate position may have from 1-20 chemicals that can be screened by administration to a well containing the interactions of interest. Thus, if modulation is detected, smaller and smaller pools of interacting pairs can be assayed for the modulation activity. By such methods, many candidate molecules can be screened.

Many diversity libraries suitable for use are known in the art and can be used to provide compounds to be tested according to the present invention. Alternatively, libraries can be constructed using standard methods. Chemical (synthetic) libraries, recombinant expression libraries, or polysome-based libraries are exemplary types of libraries that can be used.

The libraries can be constrained or semirigid (having some degree of structural rigidity), or linear or nonconstrained. The library can be a cDNA or genomic expression library, random peptide expression library or a chemically synthesized random peptide library, or non-peptide library. Expression libraries are introduced into the cells in which the assay occurs, where the nucleic acids of the library are expressed to produce their encoded proteins.

In one embodiment, peptide libraries that can be used in the present invention may be libraries that are chemically synthesized in vitro. Examples of such libraries are given in Houghten et al., 1991, *Nature* 354:84-86, which describes mixtures of free hexapeptides in which the first and second residues in each peptide were individually and specifically defined; Lam et al., 1991, *Nature* 354:82-84, which describes a "one bead, one peptide" approach in which a solid phase split synthesis scheme produced a library of peptides in which each bead in the collection had immobilized thereon a single, random sequence of amino acid residues; Medynski, 1994, *Bio/Technology* 12:709-710, which describes split synthesis and T-bag synthesis methods; and Gallop et al., 1994, *J. Med. Chem.* 37:1233-1251. Simply by way of other examples, a combinatorial library may be prepared for use, according to the methods of Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; or Salmon et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712. PCT Publication No. WO 93/20242 and Brenner and Lerner,

1992, Proc. Natl. Acad. Sci. USA 89:5381-5383 describe "encoded combinatorial chemical libraries," that contain oligonucleotide identifiers for each chemical polymer library member.

In a preferred embodiment, the library screened is a biological expression library that is a random peptide phage display library, where the random peptides are constrained (e.g., by virtue of having disulfide bonding).

Further, more general, structurally constrained, organic diversity (e.g., nonpeptide) libraries, can also be used. By way of example, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) may be used.

Conformationally constrained libraries that can be used include but are not limited to those containing invariant cysteine residues which, in an oxidizing environment, cross-link by disulfide bonds to form cystines, modified peptides (e.g., incorporating fluorine, metals, isotopic labels, are phosphorylated, etc.), peptides containing one or more non-naturally occurring amino acids, non-peptide structures, and peptides containing a significant fraction of  $\gamma$ -carboxyglutamic acid.

Libraries of non-peptides, e.g., peptide derivatives (for example, that contain one or more non-naturally occurring amino acids) can also be used. One example of these are peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371). Peptoids are polymers of non-natural amino acids that have naturally occurring side chains attached not to the  $\alpha$  carbon but to the backbone amino nitrogen. Since peptoids are not easily degraded by human digestive enzymes, they are advantageously more easily adaptable to drug use. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al., 1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The members of the peptide libraries that can be screened according to the invention are not limited to containing the 20 naturally occurring amino acids. In particular, chemically synthesized libraries and polysome based libraries allow the use of amino acids in addition to the 20 naturally occurring amino acids (by their inclusion in the precursor pool of amino acids used in library production). In specific embodiments, the library members contain one or more non-natural or non-classical amino acids or cyclic peptides. Non-classical amino acids include but are not limited to the D-isomers of the common amino acids,  $\gamma$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid;  $\gamma$ -Abu,  $\gamma$ -Ahx, 6-amino hexanoic acid; Aib, 2-amino isobutyric acid; 3-amino propionic



acid; ornithine; norleucine; norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, designer amino acids such as  $\beta$ -methyl amino acids,  $\gamma$ -methyl amino acids, N-methyl amino acids, fluoro-amino acids and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

In a specific embodiment, fragments and/or analogs of complexes of the invention, or protein components thereof, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex activity or formation.

In another embodiment of the present invention, combinatorial chemistry can be used to identify modulators of a the complexes. Combinatorial chemistry is capable of creating libraries containing hundreds of thousands of compounds, many of which may be structurally similar. While high throughput screening programs are capable of screening these vast libraries for affinity for known targets, new approaches have been developed that achieve libraries of smaller dimension but which provide maximum chemical diversity. (See e.g., Matter, 1997, J. Med. Chem. 40:1219-1229).

One method of combinatorial chemistry, affinity fingerprinting, has previously been used to test a discrete library of small molecules for binding affinities for a defined panel of proteins. The fingerprints obtained by the screen are used to predict the affinity of the individual library members for other proteins or receptors of interest (in the instant invention, the protein complexes of the present invention and protein components thereof.) The fingerprints are compared with fingerprints obtained from other compounds known to react with the protein of interest to predict whether the library compound might similarly react. For example, rather than testing every ligand in a large library for interaction with a complex or protein component, only those ligands having a fingerprint similar to other compounds known to have that activity could be tested. (See, e.g., Kauvar et al., 1995, Chem. Biol. 2:107-118; Kauvar, 1995, Affinity fingerprinting, Pharmaceutical Manufacturing International. 8:25-28; and Kauvar, Toxic-Chemical Detection by Pattern Recognition in New Frontiers in Agrochemical Immunoassay, Kurtz, Stanker and Skerritt (eds), 1995, AOAC: Washington, D.C., 305-312).

Kay et al. (1993, Gene 128:59-65) disclosed a method of constructing peptide libraries that encode peptides of totally random sequence that are longer than those of any prior conventional libraries. The libraries disclosed in Kay et al. encode totally synthetic random peptides of greater than about 20 amino acids in length. Such libraries can be advantageously screened to identify complex modulators. (See also U.S. Patent



No. 5,498,538 dated March 12, 1996; and PCT Publication No. WO 94/18318 dated August 18, 1994).

A comprehensive review of various types of peptide libraries can be found in Gallop et al., 1994, J. Med. Chem. 37:1233-1251.

#### 4.7 PHARMACEUTICAL COMPOSITIONS AND THERAPEUTIC/PROPHYLACTIC ADMINISTRATION

The invention provides methods of treatment (and prophylaxis) by administration to a subject of an effective amount of a therapeutic of the invention. In a preferred aspect, the therapeutic is substantially purified. The subject is preferably an animal including, but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human. In a specific embodiment, a non-human mammal is the subject.

Various delivery systems are known and can be used to administer a therapeutic of the invention, e.g., encapsulation in liposomes, microparticles, and microcapsules; use of recombinant cells capable of expressing the therapeutic, use of receptor-mediated endocytosis (e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432); construction of a therapeutic nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion, by bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral, rectal and intestinal mucosa, etc.), and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion during surgery,

topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of a malignant tumor or neoplastic or pre-neoplastic tissue.

In another embodiment, the therapeutic can be delivered in a vesicle, in particular a liposome (Langer, 1990, *Science* 249:1527-1533; Treat et al., 1989, In: *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler, eds., Liss, New York, pp. 353-365; Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the therapeutic can be delivered via a controlled release system. In one embodiment, a pump may be used (Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201-240; Buchwald et al., 1980, *Surgery* 88:507-516; Saudek et al., 1989, *N. Engl. J. Med.* 321:574-579). In another embodiment, polymeric materials can be used (*Medical Applications of Controlled Release*, Langer and Wise, eds., CRC Press, Boca Raton, Florida, 1974; *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball, eds., Wiley, New York, 1984; Ranger and Peppas, 1983, *Macromol. Sci. Rev. Macromol. Chem.* 23:61; Levy et al., 1985, *Science* 228:190-192; During et al., 1989, *Ann. Neurol.* 25:351-356; Howard et al., 1989, *J. Neurosurg.* 71:858-863). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (e.g., Goodson, 1984, In: *Medical Applications of Controlled Release*, *supra*, Vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer (1990, *Science* 249:1527-1533).

In a specific embodiment where the therapeutic is a nucleic acid encoding a protein therapeutic, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or by coating it with lipids, cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (e.g., Joliot et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:1864-1868), etc. Alternatively, a nucleic acid therapeutic can be introduced

intracellularly and incorporated by homologous recombination within host cell DNA for expression.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a therapeutic, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated, in accordance with routine procedures, as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration



are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water or saline for injection can be provided so that the ingredients may be mixed prior to administration.

The therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free carboxyl groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., those formed with free amine groups such as those derived from isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc., and those derived from sodium, potassium, ammonium, calcium, and ferric hydroxides, etc.

The amount of the therapeutic of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for intravenous administration are generally about 20-500 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Suppositories generally contain active ingredient in the range of 0.5% to 10% by weight; oral formulations preferably contain 10% to 95% active ingredient.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of



pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. For example, the kit can comprise in one or more containers a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins listed in the fourth column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fifth column of table 1.

Alternatively, the kit can comprise in one or more containers, all proteins, functionally active fragments or functionally active derivatives thereof of from the group of proteins in the sixth column of table 1.

The kits of the present invention can also contain expression vectors encoding the essential components of the complex machinery, which components after being expressed can be reconstituted in order to form a biologically active complex. Such a kit preferably also contains the required buffers and reagents. Optionally associated with such container(s) can be instructions for use of the kit and/or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

#### 4.8 ANIMAL MODELS

The present invention also provides animal models. In one embodiment, animal models for diseases and disorders involving the protein complexes of the present invention are provided. These animal models are well known in the art. These animal models include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention. Such animals can be initially produced by promoting homologous recombination or insertional mutagenesis between genes encoding the protein components of the complexes in the chromosome, and exogenous genes encoding the protein components of the complexes that have been rendered biologically inactive or deleted (preferably by insertion of a

heterologous sequence, e.g., an antibiotic resistance gene). In a preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which a gene encoding a component protein from the fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, and a gene encoding a component protein from the fifth column of table 1, or a functionally active fragment or functionally active derivative thereof, has been inactivated or deleted (Capecchi, 1989, Science 244:1288-1292).

In another preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which the genes of all component proteins from the group of proteins listed in the fourth column of table 1 or of all proteins from the group of proteins listed in the fifth column of table 1 have been inactivated or deleted.

The chimeric animal can be bred to produce additional knockout animals. Such animals can be mice, hamsters, sheep, pigs, cattle, etc., and are preferably non-human mammals. In a specific embodiment, a knockout mouse is produced.

Such knockout animals are expected to develop, or be predisposed to developing, diseases or disorders associated with mutations involving the protein complexes of the present invention, and thus, can have use as animal models of such diseases and disorders, e.g., to screen for or test molecules (e.g., potential therapeutics) for such diseases and disorders.

In a different embodiment of the invention, transgenic animals that have incorporated and express (or over-express or mis-express) a functional gene encoding a protein component of the complex, e.g. by introducing the a gene encoding one or more of the components of the complex under the control of a heterologous promoter (i.e., a promoter that is not the native promoter of the gene) that either over-expresses the protein or proteins, or expresses them in tissues not normally expressing the complexes or proteins, can have use as animal models of diseases and disorders characterized by

elevated levels of the protein complexes. Such animals can be used to screen or test molecules for the ability to treat or prevent the diseases and disorders cited supra.

In one embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group of proteins listed in the fourth column of table 1, and an endogenous gene encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fifth column of table 1 has been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof. In addition, the present invention provides a recombinant non-human animal in which the endogenous genes of all proteins, or functionally active fragments or functionally active derivatives thereof of one of the group of proteins listed in the sixth column have been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof:

In another embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins of the fourth column of table 1, and endogenous gene encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins of the fifth column, of table 1 are recombinantly expressed in said animal or an ancestor thereof.

The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

## EXAMPLES

An object of the present invention was to identify protein complexes of the APP processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP

processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said complexes were identified. The components are listed in table 1.

APP-C59-complex, Bace1-complex, Bace2-complex, BRI-complex, mDab1-complex, Fe65L2-complex, Plit-complex, Paladin-complex, Neurotrypsin-complex, Hunc18a-complex, Telencephalin-complex, PC7-complex, TFCP2-complex, Jip1-complex, Lamezin-complex, VTRP-complex, p75-NTR-complex

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

The present invention relates to the aph-1a-complex

1. A protein complex selected from complex I and comprising

(a) at least one first protein selected from the group consisting of:

(i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,



- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and
- (b) at least one first protein selected from the group consisting of:
- (i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (ii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (v) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

- (vii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (viii) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,
- (ix) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xi) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949"

encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(xvi) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xvii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xviii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xix) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xx) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xxi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xxiii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xxvi) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxvii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxix) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxxi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxxii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1"



encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein aph-1a (SEQ ID No: 1), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'aph-1a' encoded by a nucleic acid that hybridizes to the 'aph-1a' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a

nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

- (xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,
- (xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220"

encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,



(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-32 of the following proteins:

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic

acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,

(xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

- (xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a



nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active

fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:



- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 "

encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,

(xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

(xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg"

encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,



(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing aph-1a-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a

gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions, and/or

(xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or

(xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or



- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1"

encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated

complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or



- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a

nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or

(xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or

- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22"

encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such



treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a

nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,

(xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

- (xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,
- (xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1"



encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the APP-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a

nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(iii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(iv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(v) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(vi) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP (SEQ ID No: 2), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP' encoded by a nucleic acid that hybridizes to the 'APP' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha"



encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-6 of the following proteins:

(i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or

functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a



nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing APP-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether

- (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha"

encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.



33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid

that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or

(vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or

(ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and

Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
 (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,  
 (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,  
 (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,  
 (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(viii) "LAPTM4B" (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B" encoded by a nucleic acid that hybridizes to the "LAPTM4B" nucleic acid or its complement under low stringency conditions,

(ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the APP-C59-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a



nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(ii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(iii) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,

(iv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(v) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(vi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its

complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP-C59 (SEQ ID No: 45), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP-C59' encoded by a nucleic acid that hybridizes to the 'APP-C59' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a

nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,

(vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-6 of the following proteins:

(i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.



7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a

functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,
- (ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing APP-C59-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.



27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or

(vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions, and/or

(vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta"

encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a

nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or

(vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions, and/or

(vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several



interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,
- (ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

- (vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the APP-C99-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
    - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a

nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

(iii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(iv) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,

(v) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a

nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(viii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(ix) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(x) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(xi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xv) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two



of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP-C99 (SEQ ID No: 3), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP-C99' encoded by a nucleic acid that hybridizes to the 'APP-C99' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid

that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,

(ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-15 of the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic

acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,

(ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,



- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1"

encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,



- (vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949"

encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing APP-C99-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2"



encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or

(xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or

(xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or

(xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions, and/or

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or

- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like "



encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or

(xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or

several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B "

encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the BACE1-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,



- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and
- (b) at least one first protein selected from the group consisting of:
  - (i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
  - (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
  - (iv) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
  - (v) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
  - (vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
  - (vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

- (viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (ix) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (x) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xi) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xiii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,
- (xvi) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a

nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,

(xvii) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,

(xviii) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,

(xix) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xx) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xxi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxiii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxiv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two

of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein BACE1 (SEQ ID No: 54), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'BACE1' encoded by a nucleic acid that hybridizes to the 'BACE1' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a



nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,

(ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,
- (xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,
- (xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xxi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,
- (xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2"

encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-24 of the following proteins:

(i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"



- encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,
- (xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,

- (xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xxi) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
- (xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.



18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
  - (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

- (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a

nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,

(xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,

(xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,

(xxi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,

(xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing BACE1-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity,



protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a

nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or

(v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or

(viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or

(ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or

(xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

- (xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a

nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament



for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or

(v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or

(viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin"

encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions, and/or

(xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions, and/or

(xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or



(xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2"

encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,

(ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,

(xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,

(xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,

(xxi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,

(xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of



"stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the BACE2-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,

(ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(ii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid

that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(iii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(ix) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,

(x) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xi) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein BACE2 (SEQ ID No: 63), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'BACE2' encoded by a nucleic acid that hybridizes to the 'BACE2' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a

nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,



(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-12 of the following proteins:

(i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,

(ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(v) "calsyntenin 1" (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1"

encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is

attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.



17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
  - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
  - (v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 "

encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing BACE2-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
(i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"



encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions, and/or

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament

for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

- 37 The method of No. 36 wherein said determining step comprises determining whether
- (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
  - (vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
  - (viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying



the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic

acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

- (xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the BRI-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
    - (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(ii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein BRI (SEQ ID No: 8), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'BRI' encoded by a nucleic acid that hybridizes to the 'BRI' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a



nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-2 of the following proteins:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said

second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins; or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.



23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing BRI-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or

(v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition

of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.



40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the CtnnB1-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

- (ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.
2. The protein complex according to No. 1 wherein the first protein is the protein CtnnB1 (SEQ ID No: 65), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'CtnnB1' encoded by a nucleic acid that hybridizes to the 'CtnnB1' under low stringency conditions.
3. The protein complex according to No. 1 - 2 and comprising the following proteins:
- (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
  - (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
  - (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic

acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(ix) "TCF-4" (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4" encoded by a nucleic acid that hybridizes to the "TCF-4" nucleic acid or its complement under low stringency conditions,

(x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-1 of the following proteins:



- (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (ix) "TCF-4" (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4" encoded by a

nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions,

(x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a



nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(ix) "TCF-4" (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4" encoded by a nucleic acid that hybridizes to the "TCF-4" nucleic acid or its complement under low stringency conditions,

(x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing CtnnB1-complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
(i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said



complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic

acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

(viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or

(ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions, and/or

(x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or

several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

- (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions,
- (x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the DAB1-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

- (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic



acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,

(ii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,

(iii) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,

(iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

(v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta"

encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein DAB1 (SEQ ID No: 73), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'DAB1' encoded by a nucleic acid that hybridizes to the 'DAB1' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,

- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,
- (viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,
- (x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a

nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

(xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-8 of the following proteins:

(i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,



- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,
- (viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,
- (x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 "

encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by

modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic



acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,

(vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,

(viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,

(ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,

(x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

(xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing DAB1-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
- (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a"

encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or

(vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions, and/or

(viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions, and/or

(ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions, and/or

(x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or

(xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or

(xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and/or

(xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.



29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
34. The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated

complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions, and/or

(vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions, and/or
- (x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a



nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,

(vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,

(viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,

(ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,

(x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

- (xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Fe65-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
    - (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
    - (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a

nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(ii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(iii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(iv) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,

(v) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its

complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Fe65 (SEQ ID No: 83), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Fe65' encoded by a nucleic acid that hybridizes to the 'Fe65' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic



acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-5 of the following proteins:

(i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

- (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a

nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.



16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
  - (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a

nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing Fe65-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether  
(i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a



nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions, and/or

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic

acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or

(viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or

(x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions, and/or

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such

treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,



- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,
- (xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Fe65L2-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,

(ii) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,

(iii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a

nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(iv) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,

(v) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

(vi) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,

(vii) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,

(viii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,

(ix) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(x) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,

(xi) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

- (xii) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,
- (xiii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
- (xiv) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xvii) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (xviii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55



Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Fe65L2 (SEQ ID No: 87), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Fe65L2' encoded by a nucleic acid that hybridizes to the 'Fe65L2' under low stringency conditions.
3. The protein complex according to No. 1 - 2 and comprising the following proteins:
  - (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
  - (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
  - (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,
  - (vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,

- (vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,
- (x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,
- (xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,
- (xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,
- (xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a

nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,

(xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

(xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,

(xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-19 of the following proteins:

- (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,
- (vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,
- (vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a



- nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,
- (x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,
- (xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,
- (xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,
- (xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,
- (xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

(xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,

(xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active

fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:



- (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,
- (vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,
- (vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a

nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

(x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,

(xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,

(xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,

(xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,

(xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,

(xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing Fe65L2-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity,

protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
(i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a



nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions, and/or

(vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions, and/or

(ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions, and/or

(x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions, and/or

(xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions, and/or

(xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions, and/or

- (xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15"

encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a



nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions, and/or

(vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions, and/or

(ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions, and/or

(x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions, and/or

(xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions, and/or

(xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or

- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1"

encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a

nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,

(vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,

(vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,

(ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,



- (x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,
- (xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,
- (xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,
- (xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,
- (xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2"

encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,

(xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the FKRP-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a

nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(ii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(iii) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(iv) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(v) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(vi) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(vii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(viii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(ix) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(x) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xi) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,

(xii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,

(xiii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein FKRP (SEQ ID No: 100), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'FKRP' encoded by a nucleic acid that hybridizes to the 'FKRP' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a



- nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

- (x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,
- (xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-13 of the following proteins:

- (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,

(xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,

(xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)



and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,

(xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,

(xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing FKRP-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.



25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
- (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a

nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or

(viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or

(xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
34. The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated

complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or

(ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or

(iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions, and/or

(v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or



- (vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
 (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,  
 (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a

nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

- (xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the GSK3a-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,
- (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a



nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,

(iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,

(v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,

(ii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,

(iii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,

(iv) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,

(v) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,

(vi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1"

encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,

(vii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(viii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,

(ix) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,

(x) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,

(xi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,

(xii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(xiii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xiv) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two

of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein GSK3a (SEQ ID No: 106), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'GSK3a' encoded by a nucleic acid that hybridizes to the 'GSK3a' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,
- (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,
- (iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,
- (v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a

nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,

(vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,

(vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,

(viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,

(ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,

(x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,

(xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,

(xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,



- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,
- (xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-14 of the following proteins:

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic

acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,

(iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,

(iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,

(v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,

(vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,

(vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,

(viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,

(ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,

(x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,

- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,
- (xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune "

encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.



10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,

(ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,

(iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,

(iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,

(v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,

- (vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,
- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,
- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta"

encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,

(xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,

(xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,

(xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing GSK3a-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the



presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like "

- encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and/or
- (xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.



36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions, and/or

(v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions, and/or

(vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions, and/or

- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56

gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and/or

(xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or

several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,

(ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,

(iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,

(iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,

(v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,

(vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,



- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,
- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I

alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,

(xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,

(xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the JIP1-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,

(ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,

- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,
- (iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, and
- (b) at least one first protein selected from the group consisting of: and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein JIP1 (SEQ ID No: 122), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'JIP1' encoded by a nucleic acid that hybridizes to the 'JIP1' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,
- (ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,
- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a

nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-0 of the following proteins:

(i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,

(ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,

(iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.



7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,
- (ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,
- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,
- (iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing JIP1-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions, and/or



(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,
- (ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,
- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a

nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Nicastrin-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,



- (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and
- (b) at least one first protein selected from the group consisting of:
  - (i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
  - (ii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

- (iii) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,
- (iv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (v) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vi) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (vii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (viii) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (ix) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (x) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363"

- encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xiv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,
- (xv) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xix) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

- (xx) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxi) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxiii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxiv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,
- (xxvi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxvii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA,



0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP-C99 (SEQ ID No: 3), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP-C99' encoded by a nucleic acid that hybridizes to the 'APP-C99' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a

nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,

(xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,

(xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2"



encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,

(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-27 of the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a

nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,

(xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

- (xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,
- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2"



encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

- (xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or

functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a



nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,
- (xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481"

encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,

(xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,

(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1"



encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing Nicastrin-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a

nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

(xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or



- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or
- (xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament

for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or



- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3"

encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

(xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions, and/or

- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or
- (xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or
- (xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or
- (xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21"

encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several



interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a

nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,

(xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,

(xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2"



encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,

(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the pen-2-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,

(ii) "CttnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CttnD1" encoded by a nucleic acid that hybridizes to the "CttnD1" nucleic acid or its complement under low stringency conditions,

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(ii) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,

(iii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

- (iv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (v) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (viii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (ix) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (x) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xi) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a

nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xiii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xiv) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein pen-2 (SEQ ID No: 132), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'pen-2' encoded by a nucleic acid that hybridizes to the 'pen-2' under low stringency conditions.



3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,
- (viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a

nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-17 of the following proteins:

- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a

nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,

(vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

(viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,



- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a

nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
  - (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a



nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,

(vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

(viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin"

encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing pen-2-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
 (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or

(vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions, and/or

(viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or



- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22"

encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a

nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or

(vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions, and/or

(viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or



- (xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a

nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

- (viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a



nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Psen1-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a

nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

- (i) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (ii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (iii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (iv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (v) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (viii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a

nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(ix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(x) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two



of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Nicastrin (SEQ ID No: 5), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Nicastrin' encoded by a nucleic acid that hybridizes to the 'Nicastrin' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a

nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,

(xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,

(xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25"

encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-16 of the following proteins:

(i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,



- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

- (xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a



functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090"

encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,



(xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing Psen1-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic

acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

(ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or

(x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or

(xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or

(xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or

(xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD"



encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CttnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CttnA1" encoded by a nucleic acid that hybridizes to the "CttnA1" nucleic acid or its complement under low stringency conditions, and/or

(v) "CttnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CttnA2" encoded by a

- nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25"



encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several

interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(iv) "CttnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CttnA1" encoded by a nucleic acid that hybridizes to the "CttnA1" nucleic acid or its complement under low stringency conditions,

(v) "CttnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CttnA2" encoded by a nucleic acid that hybridizes to the "CttnA2" nucleic acid or its complement under low stringency conditions,

- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a

nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,



- (xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Psen2-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,
    - (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
    - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a

nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

- (i) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (ii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (iii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (iv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (v) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (vii) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (viii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a

nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(ix) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(x) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xiii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xiv) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,

(xv) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xvi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xx) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxi) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxiii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxv) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1"



encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC; 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Psen2 (SEQ ID No: 304), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Psen2' encoded by a nucleic acid that hybridizes to the 'Psen2' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,
- (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a

nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,

(xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,

(xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

- (xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-25 of the following proteins:

- (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a



nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,

(ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1"

encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).



9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,

(ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 "

- encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25"



encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing Psen2-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481"

encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

(xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, and/or

(xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or



- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin"

encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or

(v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a

nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

(xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or



- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2"

encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or

(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such

treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,

(ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090"



- encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the PTK7-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
    - (ii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
    - (iii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
    - (iv) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
    - (v) "HIFPH3/EGLN3" (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,

(vi) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(vii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(viii) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein PTK7 (SEQ ID No: 61), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'PTK7' encoded by a nucleic acid that hybridizes to the 'PTK7' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,



- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a

nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-8 of the following proteins:

- (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,

- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
  - (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
  - (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions.
5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
  6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
  7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
  8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).



15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic

acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,

(v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,

(viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing PTK7-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a



nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or

(v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a

nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

(vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions, and/or

(viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several

interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,



- (vi) "FADS2". (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the SPPL3-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a

nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(ii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(iii) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein SPPL3 (SEQ ID No: 343), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'SPPL3' encoded by a nucleic acid that hybridizes to the 'SPPL3' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-3 of the following proteins:

- (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a

nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in



cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing SPPL3-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity,

protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a



nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity,

or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a

nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,

(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the tau-complex



1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
    - (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
    - (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
    - (ii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
    - (iii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55

Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein tau (SEQ ID No: 349), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'tau' encoded by a nucleic acid that hybridizes to the 'tau' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,

(ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,

(iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,

(iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

(v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-3 of the following proteins:

- (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.



13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing tau-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28. The method of No. 27 wherein said determining step comprises determining whether (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.



32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the

interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta"

encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the TIP60-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions, and



(b) at least one first protein selected from the group consisting of:

- (i) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (ii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,
- (iii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,
- (iv) "TCFL1/YL1" (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1" encoded by a nucleic acid that hybridizes to the "TCFL1/YL1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein TIP60 (SEQ ID No: 84), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'TIP60' encoded by a nucleic acid that hybridizes to the 'TIP60' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a

nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,

(viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-4 of the following proteins:
- (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
  - (ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,
  - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
  - (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
  - (v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions,
  - (vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
  - (vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,
  - (viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400"

encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).



9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

(i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a

nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,

(viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions, and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing TIP60-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether

- (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or



(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions, and/or

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions, and/or

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
34. The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.
37. The method of No. 36 wherein said determining step comprises determining whether

- (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "TCFL1/YL1" (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1"

encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a



nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,

(viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a

pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the X11beta-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "calsyntenin 1" (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1" encoded by a nucleic acid that hybridizes to the "calsyntenin 1" nucleic acid or its complement under low stringency conditions,

- (ii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (iii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (iv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (v) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (vi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (vii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (viii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (ix) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll,

0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein X11beta (SEQ ID No: 364), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'X11beta' encoded by a nucleic acid that hybridizes to the 'X11beta' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,



- (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a

nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-9 of the following proteins:

- (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vi) "calsyntenin 1" (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1" encoded by a nucleic acid that hybridizes to the "calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.



12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2"

encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions., and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of: (a) exposing said complex, or a cell or organism containing X11beta-complex to one or more candidate molecules; and (b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or



- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a

nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or

(xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a

nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or

(vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or

(viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or



- (xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards

bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vi) "calsyntenin 1" (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1"

encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a

drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

## 5. PROTOCOLS:

The TAP-technology, which is more fully described in EP 1 105 508 B1 and in Rigaut, et al., 1999, Nature Biotechnol. 17:1030-1032 respectively was used and further adapted as described below for protein purification. Proteins were identified using mass spectrometry as described further below.

### 5.1 Construction of TAP-tagged bait

The cDNAs encoding the complete ORF were obtained by RT-PCR. Total RNA was prepared from appropriate cell lines using the RNeasy Mini Kit (Qiagen). Both cDNA synthesis and PCR were performed with the SUPERScript One-Step RT-PCR for Long templates Kit (Life Technologies) using gene-specific primers. After 35-40 cycles of amplification PCR-products with the expected size were gel-purified with the MinElute PCR Purification Kit (Qiagen) and, if necessary, used for further amplification. Low-abundant RNAs were amplified by nested PCR before gel-purification. Restriction sites for NotI were attached to PCR primers to allow subcloning of amplified cDNAs into the retroviral vectors pIE94-N/C-TAP thereby generating N- or C-terminal fusions with the TAP-tag (Rigaut et al., 1999, Nature Biotechnol. 17:1030-1032).

The entry points (

BACE1, BACE2, APP, APP-C99, APP-C59, Psen-1, Psen-2, Nicastrin, Aph-1a, Pen-2, CtnnB1, X11-beta, Fe65, Fe65L2, DAB1, JIP1, TIP60, GSK3a, Tau, FKRP, PTK7) were tagged at the N- and/or C-terminal end.

Clones were analyzed by restriction digest, DNA sequencing and by in vitro translation using the TNT T7 Quick Coupled Transcription/Translation System (Promega inc.). The presence of the proteins was proven by Western blotting using the protein A part of the TAP-tag for detection. Briefly, separation of proteins by standard SDS-PAGE was followed by semi-dry transfer onto a nitrocellulose membrane (PROTRAN, Schleicher&Schuell) using the MultiphorII blotting apparatus from Pharmacia Biotech.



The transfer buffer consisted of 48 mM Tris, 39 mM glycine, 10% methanol and 0,0375% sodium dodecylsulfate. After blocking in phosphate-buffered saline (PBS) supplemented with 10% dry milk powder and 0,1% Tween 20 transferred proteins were probed with the Peroxidase-Anti-Peroxidase Soluble Complex (Sigma) diluted in blocking solution. After intensive washing immunoreactive proteins were visualized by enhanced chemiluminescence (ECL; Amersham Pharmacia Biotech).

## 5.2 Preparation of Virus and infection

As a vector, a MoMLV-based recombinant virus was used.

The preparation has been carried out as follows:

### 5.2.1 Preparation of Virus

293 gp cells were grown to 100% confluency. They were split 1:5 on poly-L-Lysine plates (1:5 diluted poly-L-Lysine [0.01% stock solution, Sigma P-4832] in PBS, left on plates for at least 10 min.). On Day 2, 63 microgram of retroviral Vector DNA together with 13 microgram of DNA of plasmid encoding an appropriate envelope protein were transfected into 293 gp cells (Somia, et al., 1999, Proc. Natl. Acad. Sci. USA 96:12667-12672; Somia, et al. 2000, J. Virol. 74:4420-4424). On Day 3, the medium was replaced with 15 ml DMEM + 10% FBS per 15-cm dish. On Day 4, the medium containing viruses (supernatant) was harvested (at 24 h following medium change after transfection). When a second collection was planned, DMEM 10 % FBS was added to the plates and the plates were incubated for another 24 h. All collections were done as follows: The supernatant was filtered through 0.45 micrometer filter (Corning GmbH, cellulose acetate, 431155). The filter was placed into konical polyallomer centrifuge tubes (Beckman, 358126) that are placed in buckets of a SW 28 rotor (Beckman). The filtered supernatant was ultracentrifuged at 19400 rpm in the SW 28 rotor, for 2 hours at 21 degree Celsius. The supernatant was discarded. The pellet containing viruses was resuspended in a small volume (for example 300 microliter) of Hank's Balanced Salt Solution [Gibco BRL, 14025-092], by pipetting up and down 100-times, using an aerosol-safe tip. The viruses were used for transfection as described below.

### 5.2.2 Infection

Cells that were infected were plated one day before into one well of a 6-well plate. 4 hours before infection, the old medium on the cells was replaced with fresh medium. Only a minimal volume was added, so that the cells are completely covered (e.g. 700 microliter). During infection, the cells were actively dividing.

A description of the cells and their growth conditions is given in 5.2.3

To the concentrated virus, polybrene (Hexadimethrine Bromide; Sigma, H 9268) was added to achieve a final concentration of 8 microgram/ml (this is equivalent to 2.4 microliter of the 1 milligram/ml polybrene stock per 300 microliter of concentrated retrovirus). The virus was incubated in polybrene at room temperature for 1 hour. For infection, the virus/polybrene mixture was added to the cells and incubated at 37 degree Celsius at the appropriate CO<sub>2</sub> concentration for several hours (e.g. over-day or over-night). Following infection, the medium on the infected cells was replaced with fresh medium. The cells were passaged as usual after they became confluent. The cells contain the retrovirus integrated into their chromosomes and stably express the gene of interest.

### 5.2.3 Cell lines

The following cell lines were used:

For expression, SKN-BE2 cells were used. SKN-BE2 cells (American Type Culture Collection-No. CRL-2271) were grown in 95% OptiMEM + 5% iron-supplemented calf serum.

LAN-cells (human neuroblastoma cells) were grown in 90% RPMI 1640 + 10% FBS

The expression pattern of the TAP-tagged proteins was checked by immunoblot-analysis as described in 5.3.3 and/or by immunofluorescence as described in 5.3.1 or 5.3.2.

### 5.3 Checking of expression pattern of TAP-tagged proteins

The expression pattern of the TAP-tagged protein was checked by immunoblot analysis and/or by immunofluorescence. Immunofluorescence analysis was either carried out according to section 5.3.1 or to section 5.3.2 depending on the type of the TAP-tagged protein. Immunoblot analysis was carried out according to section 5.3.3.

#### 5.3.1 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for plasma membrane and ER bound proteins

Cells were grown in FCS media on polylysine coated 8 well chamber slides to 50% confluency. Then fixation of the cells was performed in 4% ParaFormAldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4). The cells were incubated for 30 minutes at room temperature in 300 microliters per well. Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Blocking was performed with 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at room temperature. Incubation of the primary antibodies was performed in the blocking solution overnight at +4°C. The proper dilution of the antibodies was determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin for 2x 20 minutes at room temperature. Incubation of the secondary antibodies is performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes). Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin was used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were then washed again 2x 20 minutes at room temperature in PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories).

#### 5.3.2 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for non-plasma membrane bound proteins:

Cells were grown in FCS media on Polylysine coated 8 well chamber slides to 50% confluency. Fixation of the cells was performed in 4% ParaFormAldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4) for 30 minutes at Room Temperature (RT), 300 microliters per well. Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Permeabilization of cells was done with 0.5% Triton X-100 in PBS for 10 minutes at room temperature. Blocking was then done in 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at RT (Blocking solution). Incubation of the primary antibodies was performed in the blocking solution, overnight at +4°C. The proper dilution of the antibodies has to be determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin, for 2x 20 minutes at RT. Incubation of the secondary antibodies was performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes), Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin is used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were washed 2x 20 minutes at RT in PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories).

### 5.3.3 Immunoblot analysis

To analyze expression levels of TAP-tagged proteins, a cell pellet (from a 6-well dish) was lysed in 60  $\mu$ l DNase I buffer (5% Glycerol, 100 mM NaCl, 0.8 % NP-40 (IGEPAL), 5 mM magnesium sulfate, 100  $\mu$ g/ml DNase I (Roche Diagnostics), 50 mM Tris, pH 7.5, protease inhibitor cocktail) for 15 min on ice. Each sample was split into two aliquots. The first half was centrifuged at 13,000 rpm for 5 min. to yield the NP-40-extractable material in the supernatant; the second half (total material) was carefully triturated. 50  $\mu$ g each of the NP-40-extractable material and the total material are mixed with DTT-containing sample buffer for 30 min at 50°C on a shaker and separated by SDS polyacrylamide gel electrophoresis on a precast 4-12% Bis-Tris gel (Invitrogen). Proteins were then transferred to nitrocellulose using a semi-dry procedure with a discontinuous buffer system. Briefly, gel and nitrocellulose membrane were stacked between filter papers soaked in either anode buffer (three layers buffer A1 (0.3 M Tris-HCl) and three



layers buffer A2 (0.03 M Tris-HCl)) or cathode buffer (three layers of 0.03 M Tris-HCl, pH 9.4, 0.1 % SDS, 40 mM  $\epsilon$ -aminocaproic acid). Electrotransfer of two gels at once was performed at 600 mA for 25 min. Transferred proteins were visualized with Ponceau S solution for one min to control transfer efficiency and then destained in water. The membrane was blocked in 5% non-fat milk powder in TBST (TBS containing 0.05% Tween-20) for 30 min at room temperature. It was subsequently incubated with HRP-coupled PAP antibody (1:5000 diluted in 5% milk/TBST) for 1 h at room temperature, washed three times for 10 min in TBST. The blot membrane was finally soaked in chemiluminescent substrate (ECL, Roche Diagnostics) for 2 min. and either exposed to X-ray film or analyzed on an imaging station.

#### 5.4 Purification of protein complexes

Protein complex purification was adapted to the sub-cellular localization of the TAP-tagged protein and was performed as described below.

##### 5.4.1 Lysate preparation for cytoplasmic proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of CZ lysis buffer (50 mM Tris-Cl, pH 7.4; 5 % Glycerol; 0,2 % IGEPAL; 1.5 mM  $MgCl_2$ ; 100 mM NaCl; 25 mM NaF; 1 mM  $Na_3VO_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was incubated for 30 min on ice and spun for 10 min at 20,000g. The supernatant was subjected to an additional ultracentrifugation step for 1 h at 100,000g. The supernatant was recovered and rapidly frozen in liquid nitrogen or immediately processed further.

##### 5.4.2 Lysate preparation for membrane proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Membrane-Lysis buffer (50 mM Tris, pH 7.4; 7.5 % Glycerol; 1 mM EDTA; 150 mM NaCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 750g, the supernatant was recovered and subjected to an ultracentrifugation step for 1 h at 100,000g. The membrane pellet was resuspended in 7.5 ml of Membrane-Lysis buffer containing 0.8% n-Dodecyl- $\beta$ -D-maltoside and incubated for 1 h at 4°C with constant agitation. The sample was subjected to another ultracentrifugation step for 1 h at 100,000g and the solubilized material was quickly frozen in liquid nitrogen or immediately processed further.

#### 5.4.3 Lysate preparation for nuclear proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scraper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Hypotonic-Lysis buffer (10 mM Tris, pH 7.4; 1.5 mM  $\text{MgCl}_2$ ; 10 mM KCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 2,000g and the resulting supernatant (S1) saved on ice. The nuclear pellet (P1) was resuspended in 5 ml Nuclear-Lysis buffer (50 mM Tris, pH 7.4; 1.5 mM  $\text{MgCl}_2$ ; 20 % Glycerol; 420 mM NaCl; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and incubated for 30 min on ice. The sample was combined with S1, further diluted with 7 ml of Dilution buffer (110 mM Tris, pH 7.4; 0.7 % NP40; 1.5 mM  $\text{MgCl}_2$ ; 25 mM NaF; 1 mM  $\text{Na}_3\text{VO}_4$ ; 1 mM DTT), incubated on ice for 10 min and centrifuged at 100,000g for 1h. The final supernatant (S2) was frozen quickly in liquid nitrogen.

#### 5.4.4 Tandem Affinity Purification

The frozen lysate was quickly thawed in a 37°C water bath, and spun for 20 min at 100,000g. The supernatant was recovered and incubated with 0.2 ml of settled rabbit IgG-Agarose beads (Sigma) for 2 h with constant agitation at 4°C. Immobilized protein complexes were washed with 10 ml of CZ lysis buffer (containing 1 Complete™ tablet (Roche) per 50 ml of buffer) and further washed with 5 ml of TEV cleavage buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 0.5 mM EDTA; 1 mM DTT). Protein-complexes were eluted by incubation with 5 µl of TEV protease (GibcoBRL, Cat.No. 10127-017) for 1 h at 16°C in 150 µl TEV cleavage buffer. The eluate was recovered and combined with 0.2 ml settled Calmodulin affinity beads (Stratagene) in 0.2 ml CBP binding buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 2mM MgAc; 2mM Imidazole; 1mM DTT; 4 mM CaCl<sub>2</sub>) followed by 1 h incubation at 4°C with constant agitation. Immobilized protein complexes were washed with 10 ml of CBP wash buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 1mM MgAc; 1mM Imidazole; 1mM DTT; 2 mM CaCl<sub>2</sub>) and eluted by addition of 600 µl CBP elution buffer (10 mM Tris, pH 8.0; 5 mM EGTA) for 5 min at 37°C. The eluate was recovered in a siliconized tube and lyophilized. The remaining Calmodulin resin was boiled for 5 min in 50 µl 4x Laemmli sample buffer. The sample buffer was isolated, combined with the lyophilised fraction and loaded on a NuPAGE gradient gel (Invitrogen, 4-12%, 1.5 mm, 10 well).

#### 5.4.5 Isolation of the Sambiasin complex of the invention from mouse tissue

Two mouse forebrains (0.6314 g total wet weight) were lysed in 14 mls of 50 mM HEPES pH 7.4; 150 mM NaCl; 1 mM EDTA; 0.5 mM Sodium Vanadate; 10% Glycerol; 1% n-Dodecyl-β-D-maltoside containing standard proteinase inhibitors. The tissue was homogenised in a Warring blender for 30 seconds on ice. Homogenates were incubated on ice for 1 hour and then centrifuged at 13,000 g for 30 min at 4°C. The resulting pellet was stored at -80°C while the supernatant was centrifuged at 50,000 g for 30 min at 4°C and the resulting pellet was also stored at -80°C. 6.5 ml of the supernatant from this second centrifugation step was taken and combined with 25 µl of anti presenilin-1 antisera (MAB5232, Chemicon). The antibody/lysate mixture was incubated for 1 hour at 4°C with end-over end mixing. Pre-washed protein G sepharose was added and the

mixture was incubated overnight at 4°C with end-over mixing. The protein G was recovered by centrifugation at 200 g for 5 min at 4°C. The protein G beads were then washed 5 times in 1ml lysis buffer (containing 0.1% n-Dodecyl- $\beta$ -D-maltoside rather than 1%). 100  $\mu$ l of NuPAGE sample buffer (Invitrogen) was added and the sample incubated at 37°C for 10 min. Samples were separated on 4-12 % NuPAGE bis/tris gels (Invitrogen, 1.5 mm, 10 well). Proteins were visualized by staining with colloidal coomassie (Sigma) and then analysed by LC/MSMS.

## 5.5 Protein identification by mass spectrometry

### 5.5.1 Protein digestion prior to mass spectrometric analysis

Gel-separated proteins were reduced, alkylated and digested in gel essentially following the procedure described by Shevchenko et al., 1996, Anal. Chem. 68:850-858. Briefly, gel-separated proteins were excised from the gel using a clean scalpel, reduced using 10 mM DTT (in 5mM ammonium bicarbonate, 54°C, 45 min) and subsequently alkylated with 55 mM iodoacetamid (in 5 mM ammonium bicarbonate) at room temperature in the dark (30 min). Reduced and alkylated proteins were digested in gel with porcine trypsin (Promega) at a protease concentration of 12.5 ng/ $\mu$ l in 5mM ammonium bicarbonate. Digestion was allowed to proceed for 4 hours at 37°C and the reaction was subsequently stopped using 5  $\mu$ l 5% formic acid.

### 5.5.2 Sample preparation prior to analysis by mass spectrometry

Gel plugs were extracted twice with 20  $\mu$ l 1% TFA and pooled with acidified digest supernatants. Samples were dried in a vacuum centrifuge and resuspended in 13  $\mu$ l 1% TFA.

### 5.5.3 Mass spectrometric data acquisition



Peptide samples were injected into a nano LC system (CapLC, Waters or Ultimate, Dionex) which was directly coupled either to a quadrupole TOF (QTOF2, QTOF Ultima, QTOF Micro, Micromass or QSTAR Pulsar, Sciex) or ion trap (LCQ Deca XP) mass spectrometer. Peptides were separated on the LC system using a gradient of aqueous and organic solvents (see below). Solvent A was 5% acetonitrile in 0.5% formic acid and solvent B was 70% acetonitrile in 0.5% formic acid.

Time (min)	% solvent A	% solvent B
0	95	5
5.33	92	8
35	50	50
36	20	80
40	20	80
41	95	5
50	95	5

Peptides eluting off the LC system were partially sequenced within the mass spectrometer.

#### 5.5.4 Protein identification

The peptide mass and fragmentation data generated in the LC-MS/MS experiments were used to query fasta formatted protein and nucleotide sequence databases maintained and updated regularly at the NCBI (for the NCBI nr, dbEST and the human and mouse genomes) and European Bioinformatics Institute (EBI, for the human, mouse, *D. melanogaster* and *C. elegans* proteome databases). Proteins were identified by correlating the measured peptide mass and fragmentation data with the same data computed from the entries in the database using the software tool Mascot (Matrix Science; Perkins et al., 1999, *Electrophoresis* 20:3551-3567). Search criteria varied depending on which mass spectrometer was used for the analysis.

TABLE 1

## COMPONENTS OF COMPLEXES

Name of complex	Entry Point	All Interactors of the complex	known interactors of the complex	Novel interactors of the complex
aph-1a-complex	aph-1a	APP	APP	
		APP-C99		APP-C99
		JUP		JUP
		Nicastrin		Nicastrin
		Psen1		Psen1
		ACAT1		ACAT1
		BRI		BRI
		calsyntenin 1		calsyntenin, 1
		CGI-13		CGI-13
		CPD		CPD
		DLK1		DLK1
		DSCD75		DSCD75
		Endo180		Endo180
		FACL3		FACL3
		FLJ10579		FLJ10579
		ITM2C		ITM2C
		ITPR1		ITPR1
		KIAA0062 Zn transp		KIAA0062 Zn transp
		KIAA0363		KIAA0363
		KIAA1949		KIAA1949
		KiDins220		KiDins220
		MDR1		MDR1
		Neurotrypsin		Neurotrypsin
		PLD3		PLD3
		PP2Cg		PP2Cg
		RetSDR2		RetSDR2
		SARM		SARM
		SFXN1		SFXN1
		SORL1		SORL1
		SPC18		SPC18
		SPC22		SPC22
		SPC25		SPC25
		SPTLC2		SPTLC2
		stearoyl-CoA desaturase		stearoyl-CoA desaturase
		TMP21		TMP21
		VLCAD		VLCAD
		YME1L1		YME1L1
APP-complex	APP	APP-C99	APP-C99	
		Fe65		Fe65

		Fe65L1		Fe65L1
		BRI		BRI
		IL13RA2		IL13RA2
		ITM2C		ITM2C
		LAPTM4B		LAPTM4B
		S100alpha		S100alpha
		S100beta		S100beta
APP-C59-complex	APP-C59	Fe65	Fe65	Fe65L1
		Fe65L1		COPS3
		COPS3		Cullin-3
		Cullin-3		nardilysin
		nardilysin		S100alpha
		S100alpha		S100beta
		S100beta		visinin-like 1
		visinin-like 1		
APP-C99-complex	APP-C99	APP	APP	
		Fe65		Fe65
		Fe65L1		Fe65L1
		BRI		BRI
		Caldesmon		Caldesmon
		calsyntenin 1		calsyntenin 1
		CNIP		CNIP
		CPD		CPD
		DLK1		DLK1
		GPR49		GPR49
		IL13RA2		IL13RA2
		ITM2C		ITM2C
		KIAA1949		KIAA1949
		LAPTM4B		LAPTM4B
		Nap1-like		Nap1-like
		S100alpha		S100alpha
		S100beta		S100beta
		visinin-like 1		visinin-like 1
BACE1-complex	BACE1	APP	APP	
		Nicastrin		Nicastrin
		ACAT1		ACAT1
		APLP2		APLP2
		BRI		BRI
		calsyntenin 1		calsyntenin 1
		CELSR2		CELSR2
		CGI-13		CGI-13
		DLK1		DLK1
		DSCD75		DSCD75
		FADS2		FADS2
		GPR49		GPR49
		ITM2C		ITM2C
		KiDins220		KiDins220

		LAPTM4B		LAPTM4B
		Neurotrypsin		Neurotrypsin
		NogoA		NogoA
		OS-9		OS-9
		PDGFRB		PDGFRB
		PTK7		PTK7
		RetSDR2		RetSDR2
		S100alpha		S100alpha
		SORL1		SORL1
		stearoyl-CoA desaturase		stearoyl-CoA desaturase
		TMP21		
		UGCGL1		
BACE2- complex	BACE2	Nicastrin	Nicastrin	APLP2
		APLP2		BRI
		BRI		calsyntenin 1
		calsyntenin 1		CGI-13
		CGI-13		DLK1
		DLK1		DSCD75
		DSCD75		IL13RA2
		IL13RA2		ITM2C
		ITM2C		ODZ3
		ODZ3		PLD3
		PLD3		stearoyl-CoA desaturase
		stearoyl-CoA desaturase		TMP21
		TMP21		
BRI-complex	BRI	APP	APP	
		APP-C99		APP-C99
		CPD		CPD
		ITM2C		ITM2C
CtnnB1- complex	CtnnB1	Psen1	Psen1	
		APC		APC
		CtnnA1		CtnnA1
		CtnnA2		CtnnA2
		CtnnD1		CtnnD1
		JUP		JUP
		NCadh		NCadh
		TCF-4		TCF-4
		ArmVCF		ArmVCF
DAB1- complex	DAB1	APLP1	APLP1	
		APP		APP
		APP-C99		APP-C99
		DAB2IP		DAB2IP
		PP2a PR55a		PP2a PR55a
		CK1 delta		CK1 delta



		CRK		CRK
		FYN		FYN
		HSP105		HSP105
		PP2a cat beta		PP2a cat beta
		PP2a PR65		PP2a PR65
		S100alpha		S100alpha
		S100beta		S100beta
Fe65-complex	Fe65	TIP60	TIP60	
		APLP1		APLP1
		APLP2		APLP2
		APP		APP
		APP-C99		APP-C99
		Paladin		Paladin
		S100alpha		S100alpha
		S100beta		S100beta
		SAP62		SAP62
		visinin-like 1		visinin-like 1
Fe65L2-complex	Fe65L2	APLP2	APLP2	
		APP		APP
		APP-C99		APP-C99
		COPS1		COPS1
		COPS2		COPS2
		COPS3		COPS3
		COPS3		COPS3
		COPS4		COPS4
		COPS5		COPS5
		COPS6		COPS6
		COPS7b		COPS7b
		COPS8		COPS8
		Cullin-3		Cullin-3
		Nedd8		Nedd8
		Paladin		Paladin
		RBX1		RBX1
		RHOBTB1		RHOBTB1
		RHOBTB2		RHOBTB2
		S100alpha		S100alpha
		S100beta		S100beta
		TNRC15		TNRC15
		visinin-like 1		visinin-like 1
FKRP-complex	FKRP	CLGN	CLGN	
		DSCD75		DSCD75
		EXTL2		EXTL2
		ITM2C		ITM2C
		ITPR1		ITPR1
		KIAA0062 Zn transp		KIAA0062 Zn transp
		KiDins220		KiDins220

		Neurotrypsin		Neurotrypsin
		PP2Cg		PP2Cg
		SORL1		SORL1
		TLOC1		TLOC1
		UGCGL1		UGCGL1
		Wolframin		Wolframin
GSK3a-complex	GSK3a	Axin	Axin	
		FRAT1		FRAT1
		FRAT2		FRAT2
		rAxin1		rAxin1
		AKAP11		AKAP11
		C14orf129 (DUF727)		C14orf129 (DUF727)
		calcineurin A alpha		calcineurin A alpha
		calcineurin A beta		calcineurin A beta
		cdc37		cdc37
		DSCR1		DSCR1
		Nap1-like		Nap1-like
		PKA cat alpha		PKA cat alpha
		PKA cat beta		PKA cat beta
		PKA reg I alpha		PKA reg I alpha
		PP2a B56 gamma		PP2a B56 gamma
		PP2a cat beta		PP2a cat beta
		PP2a PR65		PP2a PR65
		TcD37/prune		TcD37/prune
JIP1-complex	JIP1	KLC1	KLC1	
		nKHC2		nKHC2
		uKHC		uKHC
Nicastrin-complex	Nicastrin	Nicastrin	Nicastrin	
		Psen1		Psen1
		aph-1a		aph-1a
		APP		APP
		CtnnA1		CtnnA1
		CtnnA2		CtnnA2
		CtnnB1		CtnnB1
		CtnnD1		CtnnD1
		JUP		JUP
		NCadh		NCadh
		ACAT1		ACAT1
		CGI-13		CGI-13
		CK2B		CK2B
		CLGN		CLGN
		ECSIT		ECSIT
		FACL3		FACL3
		FADS2		FADS2
		FLJ20481		FLJ20481
		ITM2C		ITM2C

		ITPR1		ITPR1
		KIAA0363		KIAA0363
		MDR1		MDR1
		Neurotrypsin		Neurotrypsin
		PTP LOC114971		PTP LOC114971
		RetSDR2		RetSDR2
		SFXN1		SFXN1
		SPC18		SPC18
		SPC22		SPC22
		SPC25		SPC25
		SPTLC2		SPTLC2
		stearoyl-CoA desaturase		stearoyl-CoA desaturase
		STT3		STT3
		TMP21		TMP21
		UGCGL1		UGCGL1
		visinin-like 1		visinin-like 1
		Wolframin		Wolframin
		YME1L1		YME1L1
pen-2- complex	pen-2	CtnnD1	CtnnD1	
		Nicastrin		Nicastrin
		Psen1		Psen1
		ACAT1		ACAT1
		CaMKIIa		CaMKIIa
		copine III		copine III
		FKRP		FKRP
		FLJ10579		FLJ10579
		FLJ20481		FLJ20481
		KIAA1102		KIAA1102
		KIAA1949		KIAA1949
		MDR1		MDR1
		Neurotrypsin		Neurotrypsin
		S100alpha		S100alpha
		SFXN1		SFXN1
		SPC22		SPC22
		SPC25		SPC25
		STT3		STT3
		TMP21		TMP21
		Wolframin		Wolframin
Psen1- complex	Psen1	Psen1	Psen1	
		aph-1a		aph-1a
		CtnnA1		CtnnA1
		CtnnA2		CtnnA2
		CtnnB1		CtnnB1
		CtnnD1		CtnnD1
		JUP		JUP
		NCadh		NCadh
		Nicastrin		Nicastrin

		pen-2		pen-2
		CaMKIIa		CaMKIIa
		DSCD75		DSCD75
		ECSIT		ECSIT
		FKRP		FKRP
		FLJ10579		FLJ10579
		FLJ20481		FLJ20481
		KIAA0090		KIAA0090
		MDR1		MDR1
		SARM		SARM
		SFXN1		SFXN1
		SORT1		SORT1
		SPC25		SPC25
		STT3		STT3
		TMP21		TMP21
		VLCAD		VLCAD
		YME1L1		YME1L1
Psen2-complex	Psen2	aph-1a	aph-1a	
		Nicastrin		Nicastrin
		Nicastrin		Nicastrin
		CGI-13		CGI-13
		DSCD75		DSCD75
		ECSIT		ECSIT
		FACL3		FACL3
		FADS2		FADS2
		FLJ10579		FLJ10579
		FLJ20481		FLJ20481
		ITPR1		ITPR1
		KIAA0090		KIAA0090
		MDR1		MDR1
		NicAChRa3		NicAChRa3
		PLD3		PLD3
		SFXN1		SFXN1
		SLC4A2		SLC4A2
		SORT1		SORT1
		SPC18		SPC18
		SPC22		SPC22
		SPC25		SPC25
		SPTLC2		SPTLC2
		stearoyl-CoA desaturase		stearoyl-CoA desaturase
		STT3		STT3
		TMP21		TMP21
		VLCAD		VLCAD
		Wolframin		Wolframin
		YME1L1		YME1L1
PTK7-complex	PTK7	APP	APP	
		BRI		BRI



		CELSR2		CELSR2
		DLK1		DLK1
		FADS2		FADS2
		HIFPH3/EGLN3		HIFPH3/EGLN3
		ITM2C		ITM2C
		Nap1-like		Nap1-like
		Reelin		Reelin
SPPL3-complex	SPPL3	APP-C99	APP-C99	
		APP		APP
		ECSIT		ECSIT
		Nap1-like		Nap1-like
		NicAChRa3		NicAChRa3
tau-complex	tau	14-3-3 zeta	14-3-3 zeta	
		PP2a PR55a		PP2a PR55a
		HSP105		HSP105
		PP2a cat beta		PP2a cat beta
		PP2a PR65		PP2a PR65
TIP60-complex	TIP60	BAF53	BAF53	
		Fe65		Fe65
		Fe65L1		Fe65L1
		TRRAP		TRRAP
		DLK1		DLK1
		DMAP1		DMAP1
		EP400		EP400
		TCFL1/YL1		TCFL1/YL1
X11beta-complex	X11beta	APLP1	APLP1	
		APLP2		APLP2
		APP		APP
		APP-C99		APP-C99
		calsyntenin 1		calsyntenin 1
		IL13RA2		IL13RA2
		ITM2C		ITM2C
		Neurotrypsin		Neurotrypsin
		Paladin		Paladin
		Reelin		Reelin
		RetSDR2		RetSDR2
		SORL1		SORL1
		TJP4		TJP4

TABLE 2

## INDIVIDUAL PROTEINS OF THE COMPLEXES

Protein name	SEQ ID	IPI number	Molecular weight
aph-1a	1	IPI00059964.1	28996
APP	2	IPI00006608.1	86943
APP-C99	3		11278
JUP	4	IPI00028128.1	81498
Nicastrin	5	IPI00021983.1	78411
Psen1	6	IPI00028077.1	52668
ACAT1	7	IPI00019898.3	64833
BRI	8	IPI00031821.1	30338
calsyntenin 1	9	IPI00218869.1	108670
CGI-13	10	IPI00008847.1	52917
CPD	11	IPI00027078.2	152915
DLK1	12	IPI00218210.1	32910
DSCD75	13	IPI00010292.1	23865
Endo180	14	IPI00005707.3	166655
FACL3	15	IPI00031397.1	80346
FLJ10579	16	IPI00018730.1	52118
ITM2C	17	IPI00016014.1	30224
ITPR1	18	IPI00216955.1	314758
KIAA0062 Zn transp	19	IPI00014236.2	62461
KIAA0363	20	IPI00004538.1	156999
KIAA1949	21	IPI00152853.1	73064
KiDins220	22	IPI00033429.1	197211
MDR1	23	IPI00027481.1	141463
Neurotrypsin	24	IPI00011063.2	97067
PLD3	25	IPI00163951.2	49573
PP2Cg	26	IPI00006167.1	59272
RetSDR2	27	IPI00008260.1	32964
SARM	28	IPI00007919.1	75337
SFXN1	29	IPI00009368.2	35619

SORL1	30	IPI00022608.1	248441
SPC18	31	IPI00104128.1	20625
SPC22	32	IPI00030262.2	20253
SPC25	33	IPI00220125.1	25692
SPTLC2	34	IPI00005751.1	62924
stearoyl-CoA desaturase	35	IPI00013007.2	41523
TMP21	36	IPI00028055.1	24976
VLCAD	37	IPI00163655.1	68788
YME1L1	38	IPI00099529.1	79832
Fe65	39	IPI00154492.2	77858
Fe65L1	40	IPI00023841.1	81080
IL13RA2	41	IPI00032199.1	44176
LAPTM4B	42	IPI00020093.1	31735
S100alpha	43	IPI00220412.1	10546
S100beta	44	IPI00220413.1	10713
APP-C59	45		6835
COPS3	46	IPI00025721.1	47873
Cullin-3	47	IPI00014312.1	88930
nardilysin	48	IPI00014521.1	130945
visinin-like 1	49	IPI00216313.1	22142
Caldesmon	50	IPI00221137.1	61213
CNIP	51	IPI00010625.1	59797
GPR49	52	IPI00021131.1	99998
Nap1-like	53	IPI00155244.1	44159
BACE1	54	IPI00216211.1	48212
APLP2	55	IPI00031030.1	86956
CELSR2	56	IPI00015346.1	317453
FADS2	57	IPI00183786.1	52259
NogoA	58	IPI00219209.1	106360
OS-9	59	IPI00218476.1	76295
PDGFRB	60	IPI00015902.2	124093
PTK7	61	IPI00219694.1	118392

UGCGL1	62	IPI00024466.1	177190
BACE2	63	IPI00001954.1	56180
ODZ3	64	IPI00165064.1	49073
CtnnB1	65	IPI00017292.1	
APC	66	IPI00215877.1	300455
CtnnA1	67	IPI00215948.1	102776
CtnnA2	68	IPI00030907.1	105282
CtnnD1	69	IPI00182469.2	107349
NCadh	70	IPI00015717.1	99851
TCF-4	71	IPI00164708.2	67919
ArmVCF	72	IPI00010490.1	104642
DAB1	73	IPI00123898.1	63578
APLP1	74	IPI00020012.2	72176
DAB2IP	75	IPI00045600.1	117651
PP2a PR55a	76	IPI00220836.2	52004
CK1 delta	77	IPI00011102.2	47330
CRK	78	IPI00004838.1	33872
FYN	79	IPI00031350.1	63754
HSP105	80	IPI00022080.1	96865
PP2a cat beta	81	IPI00008380.1	96865
PP2a PR65	82	IPI00101135.1	65309
Fe65	83	IPI00010843.1	77244
TIP60	84	IPI00165536.1	77244
Paladin	85	IPI00011063.2	97067
SAP62	86	IPI00017341.2	49256
Fe65L2	87	IPI00218296.2	53501
COPS1	88	IPI00156282.1	56481
COPS2	89	IPI00018813.1	51597
COPS4	90	IPI00171844.1	46269
COPS5	91	IPI00009958.3	37452
COPS6	92	IPI00163230.3	36163
COPS7b	93	IPI00033154.1	30277
COPS8	94	IPI00009480.1	23226



Nedd8	95	IPI00020008.1	9072
RBX1	96	IPI00003386.1	12274
RHOBTB1	97	IPI00001317.1	79417
RHOBTB2	98	IPI00187107.1	85137
TNRC15	99	IPI00169434.1	153494
FKRP	100	IPI00013281.1	54568
CLGN	101	IPI00183309.1	73577
EXTL2	102	IPI00002732.1	37466
ITM2C	103	IPI00016014.1	37466
TLOC1	104	IPI00019004.1	45862
Wolframin	105	IPI00008711.1	177190
GSK3a	106	IPI00028568.1	
Axin	107	IPI00005188.2	95635
FRAT1	108	IPI00023762.1	29062
FRAT2	109	IPI00075185.1	24051
rAxin1	110		92285
AKAP11	111	IPI00007411.1	210512
C14orf129 (DUF727)	112	IPI00009374.2	15648
calcineurin A alpha	113	IPI00220616.1	63068
calcineurin A beta	114	IPI00218862.1	58013
cdc37	115	IPI00013122.1	44468
DSCR1	116	IPI00215936.1	22767
PKA cat alpha	117	IPI00219591.1	40590
PKA cat beta	118	IPI00027283.1	40491
PKA reg I alpha	119	IPI00021831.1	42982
PP2a B56 gamma	120	IPI00185637.2	52625
TcD37/prune	121	IPI00166931.1	50200
JIP1	122	IPI00023133.1	77524
KLC1	123	IPI00020096.1	64786
nKHC2	124	IPI00028561.1	109495
uKHC	125	IPI00012837.1	109685
CtnnB1	126	IPI00017292.1	85497
CK2B	127	IPI00010865.1	24942

ECSIT	128	IPI00106506.1	49148
FLJ20481	129	IPI00016418.1	47655
PTP LOC114971	130	IPI00174190.1	22844
STT3	131	IPI00102885.1	80530
pen-2	132	IPI00020516.1	12029
CaMKIIa	133	IPI00098624.1	59022
copine III	134	IPI00024403.1	60131
KIAA1102	135	IPI00167860.1	123943
KIAA0090	136	IPI00167111.1	111759
SORT1	137	IPI00016022.1	92100
Psen2	138	IPI00028485.1	50140
NicAChRa3	139	IPI00007259.1	55637
SLC4A2	140	IPI00337431.3	137009
HIFPH3/EGLN3	141	IPI00004971.1	52259
Reelin	142	IPI00021018.1	388402
SPPL3	143	IPI00152440.1	42563
tau	144	IPI00025499.1	45850
14-3-3 zeta	145	IPI00021263.1	27745
BAF53	146	IPI00003627.1	47461
TRRAP	147	IPI00144399.1	434414
DMAP1	148	IPI00219919.1	53462
EP400	149	IPI00064931.1	340147
TCFL1/YL1	150	IPI00020434.1	40594
X11beta	151	IPI00017817.1	
TJP4	152	IPI00010544.2	60705

TABLE 3

## BIOCHEMICAL ACTIVITIES OF THE COMPLEXES

Name of complex	Biochemical Activity
BACE1-complex	Beta-secretase activity
BACE2-complex	Secretase activity
APP-complex	Signalling activity (regulator of transcription)
APP-C99-complex	Signalling activity (regulator of transcription)
APP-C59-complex	Signalling activity (regulator of transcription)
Psen-1-complex	Gamma-secretase activity
Psen-2-complex	Gamma-secretase activity
Nicastrin-complex	Gamma-secretase activity and assembly (trafficking)
Aph-1a-complex	Gamma-secretase activity and assembly (trafficking)
Pen-2-complex	Gamma-secretase activity and assembly (trafficking)
CtnnB1-complex	General: Beta-catenin signaling; here: complex regulating stability of beta-catenin
X11beta-complex	Regulator of APP processing and APP function
Fe65-complex	Regulator of APP processing and APP function
Fe65L2-complex	Regulator of APP turnover, processing and signaling
DAB1-complex	Regulator of APP processing and/or signaling; Upstream activator of tau phosphorylation
JIP1-complex	Regulator of APP trafficking and signaling
TIP60-complex	Regulator of transcription
GSK3a-complex	Regulation of APP processing
Tau-complex	Regulator of microtubules and vesicle transport along microtubules
FKRP-complex	Glycosyltransferase complex; role in maturation of the gamma-secretase complex
PTK7-complex	Role in neuronal signal transduction; involved in neural development and structural plasticity of the CNS; modulator of BACE function.

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**CLAIMS**

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions;and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C,



washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising the proteins selected from the proteins in table 1, third column or a homologue thereof, or a variant thereof or functionally active fragments or functionally active derivatives of said proteins, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions; wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, but 1 to the number of proteins listed in table 1, fifth column of said complex, or a homologue or a variant thereof, or a functionally active fragment or functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins of said fifth column under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

5. The complex of any of Claim 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said

second protein fused to an amino acid sequence different from the first protein or second protein.

6. The complex of Claim 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of Claim 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of Claim 1 - 7 that is involved in the biochemical activity as stated in table 3.

9. A process for preparing a complex of any of Claim 1 - 8 and optionally the components thereof comprising the following steps:

Expressing a protein of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the protein, preferably a tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.

10. The process according to Claim 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of Claim 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of a protein complex obtainable by a process according to any of Claim 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to Claim 1 (a) and

at least one of said proteins, being selected from the second group of proteins according to Claim1 (b).

14. Host cell, containing a vector comprising a construct of Claim 13 or containing several vectors each comprising at least the nucleic acid encoding at least one protein selected from the first group of proteins according to Claim1 (a) and the nucleic acid encoding at least one protein selected from the second group of proteins according to Claim1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of any of Claim1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more containers the complex of any of Claim 1 - 8, optionally together with an antibody according to Claim 17 and/or further components such as reagents and working instructions.

17. The kit according to Claim 16 for processing a substrate of a complex of any one of Claim 1 - 8.

18. The kit according to Claim 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

19. Array in which at least a complex according to any of Claim 1 - 8 and/or at least one antibody according to Claim 17 is attached to a solid carrier.

20. A process for processing a substrate of a complex of any one of Claim 1 - 8 comprising the step of bringing into contact a complex to any of Claim 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of Claim 1 - 8.

22. A pharmaceutical composition according to Claim 21 for the treatment of diseases and disorders, preferentially for diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

23. A method for screening for a molecule that binds to the complex of any one of Claim 1 - 8, comprising the following steps:

- (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex or protein.

24. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of Claim 1 - 8 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
- (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.

25. The method of Claim 24, wherein the amount of said complex is determined.

26. The method of Claim 25, wherein the activity of said complex is determined.

27. The method of Claim 25, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of



said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

28. The method of Claim 24, wherein the amount of the individual protein components of said complex are determined.

29. The method of Claim 25, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.

30. The method of any of Claim 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of Claim 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

32. A method for the production of a pharmaceutical composition comprising carrying out the method of Claim 24 - 29 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

33. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the Claim 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular

localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.

34. The method of Claim 33, wherein the amount of said complex is determined.

35. The method of Claim 33, wherein the activity of said complex is determined.

36. The method of Claim 35, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

37. The method of Claim 33, wherein the amount of the individual protein components of said complex are determined.

38. The complex of any one of Claim 1 - 8 or the antibody or fragment of Claim 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of Claim 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity or, or protein components of, said complex.

40. The method according to Claim 39, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to Claim 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42. Complex of Claim 1 - 8 and/or any of the proteins listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

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SEQUENCES

SEQ ID No: 1

MGA AVFFGCTFVAFGPAFALFLITVAGDPLRVII LVAGAFFWLVSLLLASV VWFILVHVTD  
RSDARLQYGLLIFGA AVSVLLQE VFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYVS  
GLSFGIISGVFSVINILADALGPGVVG I HGDSPYYFLTSAFLTAAIILLHTFWGVVFFDACE  
RRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQRS  
LLCRRQEDSRVMVYSALRIPPED

SEQ ID No: 2

MLPGLALLLLAAWTARALEVPTDGNAGLLAEPQIAMFCGRLNMHMNVQNGKWDS DPS  
GKTCTIDTKEGILQYCQEVYPELQITNVVEANQPVTIQNWCKRGRKQCKTHPHFVIPYR  
CLVGEFVSDALLVPDKCKFLHQERMDVCETHLHWHTVAKETCSEKSTNLHDYGMLLPC  
GIDKFRGVEFVCCPLAEESDNVDSADAEEDDSVWWGGADTDYADGSEDKVVEVAEE  
EEVAEVEEEEEADDDDEDDGDEVEEEAE E P YEEATERTTSIATTTTTTTESVEEVVREV  
CSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCM AVCGSAMS  
QSLLKTTQEPLARDPVKLP TTAASTPDAVDKYLETPGDENEHAHFQKAKERLEAKHRER  
MSQVMREWEEAERQAKNLPKADKKAVIQHFQEKVESLEQE AANERQQLVETHMARVE  
AMLNDRRRRLALENYITALQAVPPRPRHVFNMLKKYVRAEQKDRQHTLKHFEHVRMVDP  
KKA AQIRSQVMTHLRVIYERMNQSLSLYNVPAVAEEIQDEVDELLQKEQNYSDDVLAN  
MISEPRISYGNDALMPSLTETKTTVELLPVNGEFSLDDLQPWHSFGADSV PANTENEVE  
PVDARPAADRGLTTRPGSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFFAEDVGS  
NKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSIHHGVVEVDAAVTPEERHLSKMQQNGY  
ENPTYKFFEQMQN

SEQ ID No: 3

MDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSI  
HHGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No: 4

EVMNLMEQPIKVTEWQQTYTYDSGIHSGANTCVPSVSSKGIMEEDEACGRQYTLKKT  
TYTQGVPPSQGDLEYQMSTTARAKRVREAMCPGVSGEGQLALLATQVEGQATNLQRL  
AEPSQLLKSAIVHLINYQDDAELVTRALPELTKLLNDEDPVVVTKAAMIVNQLSKKEASR  
RALMGSPQLVA AVVRTMQNTSDLD TARCTTSILHNLSHHREGLLAIFKSGGIPALVRMLS



SPVESVLFYAITTLHNLLLYQEGAKMACAGRRRAQKMVPLLNNPKFLAITTDCLQLLAY  
GNQESKLIILANGGPQALVQIMRNYSYEKLLWTTSRVLKVLSVCPSNKP AIVEAGGMQA  
LGKHLTSNSPRLVQNCLWTLRNLSDVATKQEGLESVLKILVNQLSVDDVNVLT CATGTL  
SNLTCNNSKNKTLVTQNSGVEALIHAILRAGDKDDITEPAVCALRHLSRHPEAEMAQN  
SVRLNYGIPAIVKLLNQPNQWPLVKATIGLIRNLALCPANHAPLQEAAVIPRLVQLLVKAH  
QDAQRHVAAGTQQPYTDGVRMEEIVEGCTGALHILARDPMNRMEIFRLNTIPLFVQLLY  
SSVENIQRVAAGVLCELAQDKEAADAIDAEGASAPLMELLHSRNEG TATYAAAVLFRISE  
DKNP DYRKRVSVELTNSLFKHDPAAWEAAQSMIPINEPYGDDMDATYRPMYSSDVPLD  
PLEMHMDMDGDYPIDTYS DGLRPPYPTADHMLA

SEQ ID No: 5

MATAGGGSGADPGSRG LLRLLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRL LNATHQI  
GCQSSISGDTGVIHVVEKEEDLQWVLT DGNPPYMV LLESKHFT RDLMEK LKGRTSRIA  
GLAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCREIQWNSLG NGLAYEDFS  
FPIFLEDENETKVIKQCYQDHNLSQNGSAPT FPLCAMQLFSHMHAVISTATCMRRSSIQ  
STFSINPEIVCDPLSDYNVWSMLKPINTTGTLKPDDR VVVAATRLDSRSFFWNVAPGAE  
SAVASFVTQLAAAEALQKAPDVTTLP RNVMFVFFQGETFDYIGSSRMVYDMEKGKFPV  
QLENVDSFVELGQVALRTSLELWMHTDPVSQKNESVRNQVEDLLATLEKSGAGVPAVI  
LRRPNQSQPLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWL  
SPEEDLN FVTDTAKALADVATVLGRALYELAGGTNFSDTVQADPQTVTRLLYGFLIKAN  
NSWFQSILRQDLRSYLG DGPLQH YIAVSSPTNTTYVVQYALANLTGTVVNLTREQCQDP  
SKVPSENKDLYEYSWVQG PLHSNETDRLPRCVRSTARLARALSPAFELSQWSSTEYST  
WTESRWKDIRARIFLIASKELELITLVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY

SEQ ID No: 6

MTELPAPLSYFQNAQMSEDNHLSNTVRSQNDNRERQEHNDRRSLGHPEPLSNGRPQ  
GNSRQVVEQDEEEDEELTKYGA KHVIMLFVPVTL CMVVVVATIKSVSFYTRKDGQLIYT  
PFTEDTETVGQRALHSILNAAIMISVIVVMTILLV VLYKYRCYKVIHAWLISSLLLLFFFSFI  
YLGEVFKTYNVAVDYITVALLIWNFGVVG MISHWKGPLRLQQAYLIMISALMALVFIKYL P  
EWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAEG  
DPEAQRRVSKNSKYNAESTERESQDTVAENDDGGFSEEWEAQRD SHLGPHRSTPES  
RAAVQELSSSILAGEDPEERG VKLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGL  
CLTLLLLAIFKKALPALPISITFGLVFYFATDYLVQPFMDQLAFHQFYI

SEQ ID No: 7

MVGEEKMSLRNRLSKSRENPEEDEDQRNPAKESLETPSNGRIDIKQLIAKKIKLTAEAEA  
RLKPFFMKEVGSHFDDFVTNLIEKSASLDNGGCALTTFVLEGEKNNHRAKDLRAPPEQ  
GKIFIARRSLLDELLEVDHIRTIIYHMFIALLLFILSTLVVDYIDEGRLVLEFSLLSYAFGKFPT  
VVWTWWIMFLSTFSVPYFLFQHWATGYSSSHPLIRSLFHGFLFMIFQIGVLGFGPTYV  
VLAYTLPPASRFIIIFEQIRFVMKAHSFVRENVPRVLNSAKEKSSTVPIPTVNQYLYFLFAP  
TLIYRDSYPRNPTVRWGYVAMKFAQVFGCFFYVYYIFERLCAPLFRNIKQEPFSARVLVL  
CVFNSILPGVLILFLTFFAFLHCWLNAFAEMLRFGDRMFYKDWWNSTSYSNYYRTWNV  
VVHDWLYYYAYKDFLWFFSKRFKSAAMLAVFAVSAVVHEYALAVCLSFFYPVLFVLFMF  
FGMAFNFIVNDSRKKPIWNVLMWTSFLGNGVLLCFYSQEWYARQHCPLKNPTFLDYV  
RPRSWTCRYVF

SEQ ID No: 8

MVKVTFNSALAQKEAKKDEPKSGEEALIIPDAVAVDCKDPDDVVPVGQRRRAWCWCM  
CFGLAFMLAGVILGGAYLYKYFALQPDDVYYCGIKYIKDDVILNEPSADAPAALYQTIEEN  
IKIFEEEEVEFISVPVPEFADSDPANIVHDFNKKLTAYLDLNLDKCYVIPLNTSIVMPPRNL  
LELLINIKAGTYLPQSYLIHEHMOVITDRIENIDHLGFFIYRLCHDKETYKLQRRETIKGIQKR  
EASNCFAIRHFENKFAVETLICS

SEQ ID No: 9

MLRRPAPALAPAARLLLGLLCGGGVWAARVNVKHKPWLEPTYHGIVTENDNTVLLDPP  
LIALDKDAPLRFAGEICGFKIHGQNVPFDAVVVDKSTGEGVIRSKEKLDCELQKDYSFTIQ  
AYDCGKGPDGTNVKKSHKATVHIQVNDVNEYAPVFKEKSYKATVIEGKQYDSILRVEAV  
DADCSPQFSQICSYEITPDVPFTVDKDGYIKNTEKLNYGKEHQYKLTVTAYDCGKKRAT  
EDVLVKISIKPTCTPGWQGWNRIEYEPGTGALAVFPNIHLETCDPEVASVQATVELETS  
HIGKGCDRDTYSEKSLHRLCGAAAGTAELLPSPSGSLNWTMGLPTDNGHDSQVFEF  
NGTQAVRIPDGVVSVSPKEPFTISVWMRHGPFGRKKETILCSSDKTDMNRHHYSLYVH  
GCRLIFLFRQDPSEEKKYRPAEFHWKLNQVCDEEWHHYVLNVEFPSVTLYADGTSHEP  
FSVTEDYPLHPSKIETQLVVGACWQEFSGVENDNETEPVTVACAGGDLHMTQFFRGNL  
AGLTLRSGKLADKKVIDCLYTCKEGLDLQVLEDSGRGVQIQAHRSQVLTLLEGEDLGEL  
DKAMQHISYLNRSRQFPTPGIRRLKITSTIKCFNEATCISVPPVDGYVMVLQPEEPKISLSG  
VHHFARAASEFESSEGVFLFPELRIISTITREVEPEGDGAEDPTVQESLVSEEIVHDLDTC  
EVTVEGEELNHEQESLEVDMARLQQKGIEVSSSELGMTFTGVDTMASYEEVLHLLRYR  
NWHARSLDRKFKLICSELNGRYISNEFKVEVNVIHTANPMEHANHMAAQPFVHPEH

RSFVDLSGHNLANPHPFVAVHSTATVVIVVCVSSLVFMILGVFRIRAAHRRRTMRDQDTG  
KENEMDWDDSAITITVNPMEYEDQHSSEEEEEEEEEEEEESEEDGEEDDITSAESESSE  
EEEGEQGDPQNATRQQQLEWDDSTLSY

SEQ ID No: 10

MSFLIDSSIMITSQILFFGFGWLFFMRQLFKDYEIRQYVVQVIFSVTFASFCTMFELIIFEIL  
GVLNSSSRYFHWKMNL CVILLILVFMVPFYIGYFIVSNIRLLHKQRLLFSCLLWLTFMYFF  
WKLGDPPILSPKHGILSIEQLISRVGVIGVTLMALLSGFGAVNCPYTYMSYFLRNVTDTD  
ILALERRLLQTMDMIISKKKRMAMARRTMFQKGEVHNKPSGFWGMIKSVTTSASGSEN  
TLIQQEVDAL EELSRQLFLETADLYATKERIEYSKTFKGKYFNFLGYFFSIYCVWKIFMATI  
NIVFDRVGKTD PVTRGIEITVNYLGIQFDVKFWSQHISFILVGIIIVTSIRGLLITLT KFFYAI  
SSKSSNVIVLLLAQIMGMYFVSSVLLIRMSMPLEYRTIITEVLGELQFNFYHRWFDVIFLVS  
ALSSILFLYLAHKQAPEKQMAP

SEQ ID No: 11

MASGRDERPPWRLGRLLLLMCLLLLGSSARAAHIKKA EATTTTTTSAGAEAAEGQFD  
RYHEEELESALREAAAAGLPGLARLFSIGRSVEGRPLWVLRLTAGLGSLIPEGDAGPDAA  
GPDAAGPLLPGRPQVKLVGNMHGDET VSRQVLIYLARELAAGYRRGDPRLVRLNNTTD  
VYLLPSLNP DGFERAREGDCGFGDGGPSGASGRDNSRGRDLNRSFPDQFSTGEPPAL  
DEVPEVRALIEWIRRNKFVLSGNLHGGSVVASYPFDD SPEHKATGIYSKTSDDDEVFKYL  
AKAYASNHPIMKTGEPHCPGDEDETFKDGITNGAHWYDVEGGMQDYNVWANC FEIT  
LELSCCKYPPASQLRQEWENNRESLITLIEKVHIGVKGFVKDSITGSGLENATISVAGINH  
NITTGRFGDFYRLLVPGTYNLTVVLTGYMPLTVTNVVVKEGPATEVDFSLRPTVTSVIPD  
TTEAVSTASTVAIPNILSGTSSSYQPIQPKDFHHHHFPDMEIFLRRFANEYPNITRLYSLG  
KSVESRELYVMEISDNPGVHEPGEPEFKYIGNMHGNEVVGRELLNLIEYLCKNFGTDP  
EVTDLVHNTRIHLMPSPMNP DGYEKSQEGDSISVIGRNNSNFDLNRNFPDQFVQITDPT  
QPETIAVMSWMKSYPFVLSANLHGGSLVVNYPFDDDEQGLATYSKSPDDAVFQQIALS  
YSKENSQMFQGRPCKNMYPNEYFPHGITNGASWYNVPGGMQDWNYLQTNC FEVTIEL  
GCVKYPLEKELPNFWEQNRRLIQFMKQVHQGV RGFVLDATDGRGILNATISVAEINHP  
VTTYKTGDYWRLLVPGTYKITASARGYNPVTKNVTVKSEGAIQVNFTLVRSSTDSNNES  
KKGKGASSSTNDASVPTTKEFETLIKDL SAENGLESMLRSSSNLALALYRYHSYKDLSE  
FLRGLVMNYPHITNLTNLGQSTEYRHIWSLEISNKP NVSEPEEPKIRFVAGIHGNAPVGT  
ELLALAEFLCLNYKKNPAVTQLVDRTRIVIVPSLNP DGRERAQEKDCTSKIGQTNARGK  
DLDTDFTNNASQPETKAIENLIQKQDFSLSVALDGG SMLVTYPYDKPVQTVENKETLKH

LASLYANNHPSMHMGQPSCPNKSDENIPGGVMRGAEWHSGLGSMKDYSVTYGHCP  
TVYTSCCYFPSAARLPSLWADNKRSLLSMLVEVHKGVHGFVKDKTGKPI  
KVQTKEGGYFHVLLAPGVHNIIADGYQQQHSQVHVHDAASSVVIVFDT  
ELVVTVSGATMSALILTACIWCICSISNRHKDGFHRLRQHHDEYEDEIR  
MMSTGSKKS  
LLSHEFQDETDTTEEETLYSSKH

SEQ ID No: 12

MTATEALLRVLLLLLAFGHSTYGAECFPACNPQNGFCEDDNVCRCQPGWQ  
GGLCDQC  
VTSPGCLHGLCGEPGQCICTDGWDGELCDRDVRACSSAPCANNGT  
CVSLDGGGLYECS  
CAPGYSGKDCQKKDGPCVINGSPCQHGGTCVDDEGRASHASCLCPPG  
FSGNFCEIVA  
NSCTPNPCENDGVCTDIGGDFRCRCPAGFIDKTCSRPTVNCASSPCQ  
NGGTCLQHTQ  
GQAICFTILGVLTSLVVLGTVGIVFLNKCETWVSNLRYNHMLRKKKN  
LLQYNSGEDLAV  
NIIFPEKIDMTTFSKEAGDEEI

SEQ ID No: 13

MLGLLVALLALGLAVFALLDVWYLVRLPCAVLRARLLQPRVRDLLAEQ  
RFPGRVLP  
SDL  
DLLLHMNNARYLREADFARVAHLTRCGVLGALRELRAHTVLAASCA  
RHRRSLRLLEPFE  
VRTRLLGWDDRAFYLEARFVSLRDGFVCALLRFRQHLLGTSPERVVQ  
HLCQRRVEPPE  
LPADLQHWISYNEASSQLLRMESGLSDVTKDQ

SEQ ID No: 14

MGPGRPAPAPWPRHLLRCVLLLGCLHLGRPGAPGDAALPEPNVFLIF  
SHGLQG  
CLEAQ  
GGQVRVTPACNTSLPAQRWKWVSRNRLFNLTGMQCLGTGWPGTNTT  
ASLGM  
YECDR  
EALNLRWHCRTLGDQLSLLLGARTSNISKPGTLERGDQTRSGQWRIY  
GSEEDLCALPY  
HEVYTIQGNSHGKPKTIPFKYDNQWFHGTSTGREDGHLWCATTQDY  
GKDERWGFC  
PIKSNDCETFWDKDQLTDSCYQFNQSTLSWREAWASCEQQGADLLS  
ITEIHEQTYING  
LLTGYSSTLWIGLNDLDTSGGWQWSDNSPLKYLNWESDQPDNPSE  
ENCGVIRTESSG  
GWQNRDCSIALPYVCKKKPNATAEPTPPDRWANVKVECEPSWQPFQ  
GH  
CYRLQAEK  
RSWQESKKACLRGGGDLVSIHSMAELEFITKQIKQEVEELWIGLND  
LKLQMNFEWSDG  
SLVSFTHWHHPFEPNNFRDSLEDCVTIWGPEGRWNDSPCNQSLPSI  
CKKAGQLS  
QGAA  
EEDHGCRCRKGWTWHSPSCYWLGEDQVTYSEARRLCTDHGSQ  
LVTITNRFEQAFVSSLI  
YNWEGEYFWTALQDLNSTGSFFWLSGDEVMYTHWNRDQPGYSRGGC  
VALATGSAM  
GLWEVKNCTSF  
RARYICRQSLGTPVTPELPGPDPTPSLTGSCPQG  
WASDTKLRYCYKV  
FSSERLQDKKSWVQAQGACQELGAQLLSLASYYYYHHFVANMLN  
KIFGESEPEIHEQHW



FWIGLNRRDPRGGQSWRWSDGVGFSYHNFDRSRHDDDDIRGCAVLDLASLQWVAMQ  
CDTQLDWICKIPRGTDVREPDDSPQGRREWLRFQEA EYKFFEHHSTWAQAQRIC TW F  
QAELTSVHSQAELDFLSHNLQKFSRAQEQHWWIGLHTSESDGRFRWTDGSIINFISWA  
PGKPRPVGKDKKCVYMTASREDWGDQRCLTALPYICKRSNVTKETQPPDLPTTALGG  
CPSDWIQFLNKC FQVQGQEPQSRVKWSEAQFSCEQQEAQLVTITNPLEQAFITASLPN  
VTFDLWIGLHASQRDFQWVEQEPLMYANWAPGEPSPGPSGNKPTSCAVVLHSPS  
AHFTGRWDDRSCTEETHGFICQKGTDP SLSPSPAALPPAPGTELSYLN GTFRLLQKPLR  
WHDALLCESHNASLAYVPDPYTQAFLTQAARGLRTPLWIGLAGEEGSRRYSWVSEEP  
LNYVGWQDGE PQQP GGCTYVDVDGAWRTTSCDTKLQGA VCGVSSGPPPPRRISYHG  
SCPQGLADSAWIPFREHCYSFHMELL LGHKEARQRCQRAGGAVLSILDEMENVFVWE  
HLQSYEGQSRGAWLGMNFNPKGGTLVWQDNTAVNYSNWGPPGLGPSMLSHNSCYW  
IQSNSGLWRPGACTNITMGVVCKLPRAEQSSFSPSALPENPAALVVLM AVL LLL LALLTA  
ALILYRRRRQSIERGAFEGARYSRSSSSPTEATEKNILVSDMEMNEQQE

SEQ ID No: 15

MNNHVSSKPSTMKLKHTINPILLYFIHFLISLYTILTYIPFYFFSES RQEKS NR IKA KPVNSK  
PDSAYRSVNSLDGLASVLYPGCDTLDKVFTYAKNKFKNK RLLGTREVLNEEDEVQPN G  
KIFKKVILGQYNWLSYEDVFVRAFNFNGNLQMLGQKPKTNIAIFCETRAEWMIAAQACF  
MYNFQLVTLYATLG GPAIVHALNETEVTNIITSKELLQTKLKDIVSLVPRLRHIITVDGKPPT  
WSDFPKGIIVHTMAAVEALGAKAS MENQPHSKPLPSDIAVIMYTSGSTGLPKGVMISHS  
NIIAGITGMAERIPELGEEDVYIGYLPLAHVLELSAELVCLSHGCRIGYSSPQTLADQSSKI  
KKGSKGDT SMLKPTLMAAVPEIMDRIYKNVMNKVSEMSSFQRNLFILAYNYKMEQISKG  
RNTPLCDSFVFRKVR SLLGGNIRLLLCGGAPLSATTQRFMNICFC CPVGQGYGLTESAG  
AGTISEVWDYNTGRVGAPLVCCEIKLKNWEEGGYFNTDKPHPRGEILIGGQSVTMGY Y  
KNEAKTKADFS EDENGQRWLCTGDIGEFEPDGCLKIIDRKKDLVKLQAGEYVSLGKVEA  
ALKNLPLVDNICAYANSYHSYVIGFVVPNQKELTELARKKGLKGTWEELCNSCEMENEV  
LKV LSEAAISASLEKFEIPVKIRLSPEPWTPETGLVTD AFKLKRKELKTHYQADIERMYGR  
K

SEQ ID No: 16

MSRLGALGGARAGLG LLLGTAAGLGFLCLLYSQRWKRTQRHGRSQSLPNSLDYTQTS  
DPGRHVMLLRAPVGGAGDASVLP SLPREGQEKVLDRLDFVLTSLVALRREVEELRSSL  
RGLAGEIVGEVRCHMEENQRVARRRRRFPFVRERSDSTGSSSVYFTASSGATFTDAESE  
GGYTTANAESDNERDSDKESEDEGEDEVSCETVKMGRKDSL DLEEEAASGASSALEAG

GSSGLEDVLP LLQQADELHRGDEQGKREGFQ LLLNNKLVYGSRQDFLWRLARAYS DM  
CELTEEVSEKKS YALDGKEEAEAALEKGDESADCHLWYAVLCGQLAEHESIQRRIQSGF  
SFKEHVDKAIALQPENPMAHFLLGRWCYQVSHLSWLEKKTATALLSPLSATVEDALQS  
FLKAEELQPGFSKAGR VYISKCYRELGKNSEARWWMKLAL ELPDVT KEDLAIQKDLEEL  
EVILRD

SEQ ID No: 17

MVKISFQPAVAGIKGDKADKASASAPASATEILLTPAREEQPPQHRSKRGGSVGGVC  
YLSMGMVVLLMGLVFASVYIYRYFFLAQLARDNFFRCGVLYEDSLSSQVRTQMELEED  
VKIYLDENYERINVPVPQFGGGDPADIIHDFQRGLTAYHDISLDKCYVIELNTTIVLPPRNF  
WELLMNVKRGTYLPQTYIIQEEMVVTEHVSDKEALGSFIYHLCNGKDTYRLRRRATRRR  
INKRGAKNCNAIRHFENTFVVETLICGVV

SEQ ID No: 18

MSDKMSSFLHIGDICS LYAEGSTNGFISTLGLVDDRCVVQPETGDLNNPPKKFRDCLFK  
LCPMNRYSAQKQFWKAAKPGANSTTDAVLLNKLHHAADLEKKQNETENRKLLGTVIQY  
GNVIQLLHLKSNKYLT VNKRLPALLEKNAMRVTLDEAGNEGSWFYIQPFYKLRSIGDSV  
IGDKVVLNPVNAGQPLHASSHQLVDNPGCNEVNSVNCNTSWKIVLFMKWSDNKDDILK  
GGDVVRLFHAEQEKFLT CDEHRKKQH VFLRTTGRQSATSATSSKALWEVEVVQHDPC  
RGGAGYWNSLFRFKHLATGHYLA AEVDPDFEEECLEFQPSVDPDQDASRSRLRNAQE  
KMVYSLVSVPEGNDISSIFELDPTTLRGGDSLVRNSYVRLRHLCNTWVHSTNIPIDKE  
EEKPVMLKIGTSPVKEDKEAFAIVPVSPA EVRDLDFANDASKVLGSIAGKLEKGTITQNE  
RRSVTKLLEDLVYFVTGGTNSGQDVLEVVF SKPNRERQKLMREQNILKQIFKLLQAPFT  
DCGDGPMLRLEELGDQRHAPFRHICRLCYRVLRHSQQDYRKNQEYIAKQFGFMQKQI  
GYDVLAEDTITALLHNNRKLLEKHITAAEIDTFVSLVRKNREPRFLDYLS DLCVSMNKSIP  
VTQELICKAVLNPTNADILIETKLVL SRFEFEGVSSTGENALEAGEDEEEVWLFWRDSNK  
EIRSKSVRELAQDAKEGQKEDRDVLSYYRYQLNLFARMCLDRQYL AINEISGQLDVDLIL  
RCMSDENLPYDLRASFCRLMLHMHVDRDPQE QVTPVKYARLWSEIPSEIAIDDYDSSG  
ASKDEIKERFAQTMEFVEEYLRDVVCQRFPFSDKEKNKLT FEVVNLARNLIYFGFY NFS  
DLLRLTKILLAILDCVHVTTIFFISKMAKGEENKGNNDVEKLKSSNVMRSIHGVGELMTQV  
VLRGGGFLPMTPMAAAPEGNVKQAEPEKEDIMVMDTKLKIIELQFILNVRLDYRISCLLCI  
FKREFDESNSQTSETSSGNSSQEGPSNVP GALDFEHIEEQAEGIFGGRKVYFHEENTP  
LDLDDHGGRTFLRVLLH LTMHDYPPLVSGALQLLFRHFSQRQEV LQAFKQVQLLVTSQ  
DVDNYKQIKQDLDQLRSIVEKSELWVYKGQGPDETMDGASGENEHKKTEEGNNKPQK

HESTSSYNYRVVKEILIRLSKLCVQESASVRKSRKQQQRLLRNMGAAHVLELLQIPYEK  
 AEDTKMQEIMRLAHEFLQNFCAGNQQNQALLHKKHINLFLNPGILEAVTMQHIFMNNFQL  
 CSEINERVVQHFVHCIETHGRNVQYIKFLQTIVKAEGKFIKKCQDMVMAELVNSGEDVLV  
 FYNDRASQTLIQMMRSEDRMDENSPLMYHIHLVELLAVCTEGKNVYTEIKCNSLLPL  
 DDIVRVVTHEDCIPEVKIAYINFLNHCYVDTEVEMKEIYTSNHMWKLFENFLVDICRACNN  
 TSDRKHADSIKEYVTEIVMSIVTTFFSSPFSDQSTTLQTRQPVFVQLLQGVFRVYHCNW  
 LMPSQKASVESCIRVLSDVAKSRAIAIPVDLDSQVNNLFLKSHSIVQKTAMNWRLSARNA  
 ARDSVLAASRDYRNIIERLQDIVSALEDRLRPLVQAELSVLVDVLHRPELLFPENTDAR  
 RKCESGGFICKLIKHTKQLLEENEEKLCIKVLQTLREMMTKDRGYGEKLISIDELDNAELP  
 PAPDSENATEELEPSPPLRQLEDHKRGEALRQVLVNRYYGNVRPSGRRESLTSFGNGP  
 LSAGGPGKPGGGGGGGSGSSSMSRGEMSLAEVQCHLDKEGASNLVIDLIMNASSDRVF  
 HESILLAIALLGEGNTTIQHSFFCRLTEDKKSEKFFKVIFYDRMKVAQQEIKATVTVNTSDL  
 GNKKKDDEVDRDAPSRKKAKEPTTQITEEVRDQLLEASAATRKAFTTFRREADPDDHY  
 QPGEGTQATADKAKDDLEMSAVITIMQPILRFLQLLCENHNRLDQNLRCQNNKTNYNL  
 VCETLQFLDCICGSTTGGLGLLGLYINEKNVALINQTLLESLTEYCQGPCHENQNCIATHE  
 SNGIDIITALILNDINPLGKKRMDLVLELKAKNASKLLLAIMESRHDSENAERILYNMRPKE  
 LVEVIKKAYMQGEVEFEDGENGEDGAASPRNVGHNIYILAHQLARHNKELQSMLKPGG  
 QVDGDEALEFYAKHTAQIEIVRLDRTMEQIVFPVPSICEFLTKE SKLRIYYTTERDEQGSK  
 INDFFLRSEDLFNEMNWQKKLRAQPVLYWCARNMSFWSSISFNLAVLMNLLVAFFYPF  
 KGVRRGGTLEPHWSGLLWTAMLISLAIVIALPKPHGIRALIASTILRLIFSVGLQPTLFLLGAF  
 NVCNKIIFLMSFVGNCGTFTRGYRAMVLDVEFLYHLLYLVICAMGLFVHEFFYSLLLFDLV  
 YREETLLNVIKSVTRNGRSIILTAVLALILVYLFSIVGYLFFKDDFILEVDRLPNETAVPETG  
 ESLASEFLFSDVCRVESGENCSPAPREELVPAEETE QDKEHTCETLLMCIVTVLSHGL  
 RSGGGVGDVLRKPSKEEPLFAARVIYDLLFFFMVIIIIVLNLIFGVIIDTFADLRSEKQKKEEI  
 LKTTCFICGLERDKFDNKTVTFEEHIKEEHNMWHYLCFIVLVKVKDSTEYTGPE SYVAEM  
 IKERNLDWFPRMRAMSLVSSDSEGEQNELRNLQEKLESTMKLVTNLSGQLSELKDQMT  
 EQRKQKQRIGLLGHPPHMNVNPQQPA

SEQ ID No: 19

MKDGSGRRPQPGRGAGGRRLASRACARCRGPDVAVRGV GARVYADAPAKLLLPPPA  
 AWDLAVRLRGAEAAASERQVYSVTMKLLLLHPAFQSCLLLTLLGLWRTTPEAHASSLGAP  
 AISAASFLQDLIHRYGEGDSLTLQQLKALLNHLDVGVGRGNVTQHVQGHRLSTCFSSG  
 DLFTA HNFSEQSRIGSSELQEF CPTILQQLD SRACTSENQENEENEQTEEGRPSAVEV  
 WGYGLLCVTVISLCSLLGASVVPFMKKTFYKRLLLYFIALAIGTLYSNALFQLIPEAFGFNP



LEDYYVSKSAVVFGGFYLFFFTEKILKILLKQKNEHHHGHSHYASESLPSKKDQEEGVM  
EKLQNGDLDMIPQHCSSELDGKAPMVDEKVIVGSLSVQDLQASQSACYWLKGVRY  
DIGTLAWMITLSDGLHNFIDGLAIGASFTVSVFQGI STSVAILCEEFPHELGD FVILLNAGM  
SIQQALFFNFLSACCCYLGLAFGILAGSHFSANWIFALAGGMFLYISLADMFP EMNEVCQ  
EDERKGSILIPFIQNLGLLTGFTIMVVLTMYSGQIQIG

SEQ ID No: 20

EPCALTPGPSHLALTFLPSKPGARPQPEGASWDAGPGGAPSAWADPGEGGPSPMLLP  
EGLSSQALSTEAPLPATLEPRIVMGEETCQALLSPRAARTALRDQEGGHASPDPPPELC  
SQGDLSVPSPPDPDSFFTPSTPTKTTYALLPACGPHGDARDSEAELRDEL LDSPPAS  
PSGSYITADGDSWASSPSCSL SLLAPAEGLD FPSGWGLSPQGSMVDERELHPAGTPE  
PPSSESSL SADS SSSWGQEGHFFDLDFLANDPMIPAALLPFQGS LIFQVEAVEVTPLSP  
EEEEEEAVADPD PGGDLAGEGEEDSTSASFLQSLSDLSITEGMDEAFAFRDDTSAASS  
DSDSASYAEADDERLYSGEPHAQATLLQDSVQKTEEESGGGAKGLQAQDGT VSWAVE  
AAPQTS DRGAYLSQRQELISEVTEEGLALGQESTATVTPHTLQVAPGLQVEVATRVTPQ  
AGEEETDSTAGQESAAMAMPQPSQEGISEILGQESVTA EKLPTPQEETSLTLCPDSPQ  
NLKEEGGLDLPSGRKPVAAATIVPRQAKEDLTLPQDSAMTPPLPLQD TD LSSAPKPVAA  
ATIVSQQAE EGLTL PQDSVMTPPLPLQDTELSSAPKPVAAATLV SQQAE EGLTL PQDSA  
MTPPLPLQD TD LSSAPKPVAAATLV SQQAE EGLTL PQDSAMTPPLPLQD TD LSSAPKPV  
AAATLV SQQAE EGLTL PQDSAMTPPLPLQD TD LSSAPKPVAAATIV SQQAE EGLTL PQD  
SAMTPPLPLQD TD LSSAPKPVAAATIV SQQAE EGLTL PQDSAMTPPLPLQD TD LSSAPK  
PVAAATPV SQQAE EGLTL PQDSAMTPPLPLQD TD LSSAPKPVAAATPV SQQAE EGLTL  
PQDSAMTAPLPLQD TGPTSGPEPLAVATPQTLQAEAGCAPGTEPVATMAQQEVGEAL  
GPRPAPEEKNAALPTVPEPAALDQVQQDDPQPA AEAGTPWAAQEDADSTLGMEALSL  
PEPASGAGEEIAEALSRPGREACLEARAHTGDGAKPDSPQKETLEVENQQEGGLKLLA  
QEHGPRSALGGAREVPDAPPAACPEVSQARLLSPAREERGLSGKSTPEPTLPSAVATE  
ASLDSCPESSVGAVSSLD RGCPDAPAPTSAPTSQQPEPVLGLGSVEQPHEVPSVLGTP  
LLQPPENLAKGQPSTPVDRPLGPDPSAPGTLAGAALPPLEPPAPCLCQDPQEDSVEDE  
EPPGSLGLPPPQAGVQPA AAAVSGTTQPLGTGPRVSLSPHSPLLSPKVASMDAKDLAL  
QILPPCQVPPPSGPQSPAGPQGLSAPEQQEDED SLEEDSPRALGSGQHSDSHGESSA  
ELDEQDILAPQTVQCPAQAPAGGSEETIAKAKQSRSEKKARKAMSKLGLRQIQGVTRITI  
QKSKNILFVIAKPDVFKSPASDTYVVFGEAKIEDLSQQVHKAAA EKFKVPSEPSALVPES  
APRPRVRLECKEEEEEEEEEEVDEAGLELRDIELVMAQANVSRAKAVRALRDNHSDIVNA  
IMELTM



SEQ ID No: 21

PLCPALCPTSPPLPLLLPPSVSPPGCLTLWSLSFLFSVPSAPYPHLKTMMATIPDWKLQL  
LARRRQEEASVRGREKAERERLSQMPAWKRGLLERRRAKLGLSPGEPSPVLGTVEAG  
PPDPDEŠAVLLEAIGPVHQNRFIRQERQQQQQQQQQRSEELLAERKPGPLEARERRPSP  
GEMRDQSPKGRESREERLSPRETRERRRLGIGGAQELSLRPLEARDWRQSPGEVGDERS  
SRLSEAWKWRLSPGETPERSLRLAESREQSPRRKEVESRLSPGESAYQKLGLTEAHK  
WRPDSRESQEQSLVQLEATEWRLRSGEERQDYSEECGRKEEWPVPGVAPKETAELS  
ETLTREAQGNSSAGVEAAEQRPVEDGERGMKPTEGWKWTLSNGKAREWTPRDIEAQ  
TQKPEPPESAELLESPPGVEAGEGEGAEKEEAGAQRPLRALQNCCSVPSPLPPEDAGT  
GGLRQQEEEEAVELOPPPPAPLSPPPPAPTAPQPPGDPLMSRLFYGVKAGPGVGAPRR  
SGHTFTVNPRRSVPPATPATPTSPATVDAAVPGAGKKRYPTAEELVLGGYLRLSRSL  
AKGSPERHHKQLKISFSETALETYQYPSESSVLEELGPEPEVPSAPNPAAQPDDEED  
EEELLLLQPELQGGGLRTKALIVDESCRR

SEQ ID No: 22

LQLSVKMSVLISQSVINYVEEENIPALKALLEKCKDVDERNECGQTPLMIAAEQGNLEIVK  
ELIKNGANCNLEDLDNWTALISASKEGHVHIVEELLKCGVNLEHRDMGGWTALMWACY  
KGRTDVVELLSSHGANPSVTGLYSVYPIIWAAGRGHADIVHLLLQNGAKVNCSDKYGTT  
PLVWAARKGHLECVKHLLAMGADVQEGANSMTALIVAVKGGYTQSVKEILKRNPVN  
LTDKDGNTALMIASKEGHEIVQDLLDAGTYVNIPDRSGDTVLIQAVRGGHVEIVRALLQ  
KYADIDIRGQDNKTALYWAVEKGNATMVRDILQCNPDTEICTKDGETPLIKATKMRNIEV  
VELLLDKGAKVSAVDKKGDTPLHIAIRGRSRKLAELLRNPKDGRLLYRPNKAGETPYNI  
DCSHQKSILTQIFGARHLSPTETDGDMLGYDLYSSALADILSEPTMQPPICVGLYAQWG  
SGKSFLLKKLEDEMKTFAQQIEPLFQFSWLIVFLTLLCGGLGLLFAFTVHPNLGIAVSL  
SFLALLYIFFIVIYFGGRREGESWNWAWVLSTRLARHIGYLELLLKLMFVNPPPELPEQTTK  
ALPVRFLFTDYNRLSSVGGETSLAEMIATLSDACEREFGLATRLFRVFKTEDTQGKKK  
WKKTCCLPSFVIFLFIIGCIISGITLLAIFRVDPKHLTVNAVLISIASVVGLAFVLNCRWWQ  
VLDSLLNSQRKRLHNAASKLHKLKSEGFMKVLKCEVELMARMAKTIDSFTQNQTRLVVII  
DGLDACEQDKVLQMLDTRVFLFSKGPFIASFDPHIIKAINQNLNSVLRDSNINGHDYM  
RNIVHLPVFLNSRGLSNARKFLVTSATNGDVPCSDTTGIQEDADRRVSQNSLGEMTKLG  
SKTALNRRDITYRRRQMQRTITRQMSFDLTKLLVTEDWFSDISPQTMRRLLNIVSVTGRL  
LRANQISFNWDRLASWINLTEQWPYRTSWLILYLEETEGIPDQMTLKTIERISKNIPTTK  
DVEPLLEIDGDIRNFEVFLSSRTPVLVARDVKVFLPCTVNLDPKLREIADVRAAREQISIG

GLAYPPLPLHEGPPRAPSGYSQPPSVCSSTSFNPGFAGGVVSPQPHSSYYSGMTGPQ  
HPFYNRPFAPYLYTPRYYPGGSQHLISRPSVKTS�PRDQNNGLEVIKEDAAEGLSSPT  
DSSRGSGPAPGPVLLNSLNDVAVCEKQIEGLDQSMPLQYCTTIKKANINGRVLAQC  
NIDELKKEMNMNFGDWHLFRSTVLEMRNAESHVVPEDPRFLSESSSGPAPHGEPARR  
ASHNELPHTELSSQTPYTLNFSFEELNTLGLDEGAPRHSNLSWQSQTRRTPSLSSLNS  
QDSSIEISKLTQVQAEYRDAYREYIAQMSQLEGGPGSTTISGRSSPHSTYYMGQSSSG  
GSIHSNLEQEKGDSEPDPDDGRKSFLMKRGDVIDYSSSGVSTNDASPLDPITEEDEKS  
DQSGSKLLPGKKSSERSSLFQTDLKLKGSGLRYQKLPSEDESGTEESDNTPLLKDDK  
DRKAEGKVERVPKSPEHSAEPIRTFIKAKEYLSDALDKKDSSDSGVRSSSESSPNHSLH  
NEVADDSQLEKANLIELEDDSHSGKRGIPHSLSGLQDPHARMSCSEDKKSPSECSLIAS  
SPEENWPACQKAYNLNRTPTSTVTLNNSAPANRANQNFDEMEGIRETSQVILRPSSSP  
NPTTIQENENLKSMTHKRSQRSSYTRLKDPPELHAAASSESTGFGEERESIL

SEQ ID No: 23

MDLEGDRNGGAKKKNFFKLNNKSEKDKKEKKPTVSVFSMFRYSNWLDKLYMVVGTLA  
AIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDINDTGFFMNLEEDMTRYAYY  
YSGIGAGVLVAAYIQVSFWCLAAGRQIHKIRKQFFHAIMRQEIGWFDVHDVGELNTRLTD  
DVSKINEGIGDKIGMFFQSMATFFTGFIVGFTRGWKLTVLILAISPVGLLSAAVWAKILSSF  
TDKELLAYAKAGAVAEVLAAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIGA  
AFLLIYASYALAFWYGTTLVLSGEYSIGQVLTVFFSVLIGAFSVGQASPSIEAFANARGAA  
YEIFKIIDNKPSIDSYSGHKKPDNIKGNLEFRNVHFSYPSRKEVKILKGLNLKVQSGQTV  
ALVGNSGCGKSTTVQLMQRLYDPTEGMVSVGDQDIRTINVRFLREIIGVVSQEPVLFAT  
TIAENIRYGRENVTMDEIEKAVKEANAYDFIMKLPHKFDTLVGERGAQLSGGQKQRIAIA  
RALVRNPKILLLDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNADVIAGFDD  
GVIVEKGNHDELMKEKGIYFKLVMTAGNEVELENAADESKSEIDALEMSSNDSRSSLI  
RKRSTRRSVRGSQAQDRKLSTKEALDESIPPVSFWRIMKLNLTWPYFVVGVFCAIING  
GLQPAFAIIFSKIIGVFTRIDDPETKRQNSNLFSLFLALGIISFITFFLQGFTFGKAGEILTK  
RLRYMVFRSMLRQDVSWFDDPKNTTGALTTRLANDAAQVKGAIGSRLAVITQNIANLGT  
GIIISFIYGWQLTLLLLAIVPIIAIAGVVEMKMLSGQALKDKKELEGAGKIAIEAENFRTVVS  
LTQEQKFEHMYAQSLQVPYRNSLRKAHIFGITFSFTQAMMYFSYAGCFRFGAYLVAHKL  
MSFEDVLLVFSVAVVFGAMAVGQVSSFAPDYAKAKISAHHIIMIEKTPLIDSYSTEGLMPN  
TLEGNVTFGEVVFNYPTRPDIPVLQGLSLEVKKGQTLALVGSSGCGKSTVVQLLERFYD  
PLAGKVLLDGKEIKRLNVQWLRAHLGIVSQEPILFDCSIAENIAYGDNSRVVSQEEIVRAA  
KEANIHAIESLPNKYSTKVGDKGTQLSGGQKQRIAIAARALVRQPHILLLDEATSALDTESE

EKVVQEALDKAREGRTCIVIAHRLSTIQNADLIVVFQNGRVKEHGTHQQLLAQKGIYFSM  
VSVQAGTKRQ

SEQ ID No: 24

MTLARFVLALMLGALPEVVGFDVLNDSLHSHRHSPAGPHYYPYLPTQQRPPRTRP  
PPPLPRFPRPPRALPAQRPHALQAGHTPRPHPWGPCPAGEPWVSVTDFGAPCLRWAE  
VPPFLERSPPASWAQLRGQRHNFRCRSPDGAGRPWCFYGDARGKVDWGYCDCRHGS  
VRLRGGKNEFEGTVEVYASGVWGTVCSSHWDDSDASVICHQLQLGGKGIKQTPFSG  
LGLIPIYWSNVRRCRGDEENILLCEKDIWQGGVCPQKMAAAVTCSFSHGPTFPIIRLAGGS  
SVHEGRVELYHAGQWGTVCDDQWDDADADEVICRQLGLSGIAKAHQAYFGEGSGPV  
MLDEVRCTGNELSIEQCPKSSWGEHNCGHKEDAGVSCTPLTDGVIRLAGGKGSHEGR  
LEVYYRGQWGTVCDDGWTELNTYVVCRLGLFKYKQASANHFEESTGPIWLDDVSCS  
GKETRFLQCSRRQWGRHDCSHREDVSIACYPGGEGHRLSLGFPVRLMDGENKKEGR  
VEVFINGQWGTICDDGWTDKDAAVICRQLGYKGPARTMAYFGEGKGPIHVDNVKCT  
GNERSLADCIKQDIGRHNCRHSEDAGVICDYFGKKASGNSNKESSLSSVCGLRLLHRRQ  
KRIIGGKNSLRGGWPWQVSLRLKSSHGDGRLLCGATLLSSCWVLTAAHCFKRYGNSTR  
SYAVRVGDYHTLVPEEFEEEEIGVQQIVIHREYRPDRSDYDIALVRLQGPEEQCARFSSH  
VLPACLPLWRERPQKTASNCYITGWGDTGRAYSTRTLQQAAPLLPKRFCEERYKGRFT  
GRMLCAGNLHEHKRVDSCQGDSSGGLMCERPGEWVVGVTWGYGCGVKDSPGV  
YTKVSAFVPWIKSVTKL

SEQ ID No: 25

LAVVGFGALMTQLFLWEYGDLHLFGPNQRPAPCYDPCEAVLVESIPEGLDFPNASTGN  
PSTSQAWLGLLAGAHSSLDIASFYWTLTNNDTHTQEPSAQQGEEVLRQLQTLAPKGVN  
VRIAVSKPSGPQPQADLQALLQSGAQVRMVDQMQLTHGVLHTKFWVVDQTHFYLGSA  
NMDWRSALTQVKELGVVMYNCSCCLARDLTKIFEAYWFLGQAGSSIPSTWPRFYDTRYN  
QETPMEICLNGTPALAYLASAPPPLCPSGRTPDLKALLNVVDNARSFIYVAVMNYLPTLE  
FSHPHRFWPAIDDGLRRATYERGVKVRLLISCWGHSEPSMRAFLLSLAALRDNHTHSDI  
QVKLFVVPADAEQARIPYARVNHNKYMVTERATYIGTSNWSGNYFTETAGTSLLVTQN  
GRGGLRSQLEAIFLRDWDSPYSHDLDTADSVDGNACRLL

SEQ ID No: 26

MGAYLSQPNTVKCSGDGVGAPRLPLPYGFSAMQGWVRVSMEDAHNCIPELDSETAMFS  
VYDGHGGEEVALYCAKYLPDIKDQKAYKEGKLQKALEDAFLAIDAKLTTEEVIKELAQIA



GRPTEDEDEKEKVADEDDVDNEEAALLHEEATMTIEELLTRYGQNCHKGPPHSKSGGG  
TGEEPGSQGLNGEAGPEDSTRETPSQENGPTAKAYTGFSSNSERGTEAGQVGEPGIP  
TGEAGPSCSSASDKLPRVAKSKFFEDSEDESDEAEEDSEECSEEDGYSSEEAEN  
EEDEDDTEEAEEEDDEEEEEEMMVPGMEGKEEPGSDSGTTAVVALIRGKQLIVANAGDS  
RCVVSEAGKALDMSYDHKPEDEVELARIKNAGGKVTMDGRVNGGLNLSRAIGDHFYKR  
NKNLPPEEQMISALPDIKVLTLTDDHEFMVIACDGIWNVMSSQEVVDFIQSKISQRDENG  
ELRLLSSIVEELLQCLAPDTSGDGTGCDNMTCHICFKPRNTAELQPESGKRKLEEVLT  
EGAEENGNSDKKKKAKRD

SEQ ID No: 27

MKFLLDILLLLPLLIVCSLESFVKLFIPKRRKSVTGEIVLITGAGHGIGRLTAYEFAKLKSKL  
VLWDINKHGLEETAACKCKGLGAKVHTFVVDCCSNREDIYSSAKKVKAIEIGDVSILVNNAGV  
VYTSDLFATQDPQIEKTFEVNVLAFHWTTKAFLPAMTKNNHGHIVTVASAAGHVSVPFLL  
AYCSSKFAAVGFHKTLTDELAALQITGVKTTCLCPNFVNTGFIKNPSTSLGPTLEPEEVV  
NRLMHGILTEQKMIFIPSSIAFLTTLERILPERFLAVLKRKISVKFDAVIGYKMKQAQ

SEQ ID No: 28

MGAVARAHGGLRVARARES VAGGRHRGAGRPGARAAGAAAGLVRAEAGGRRAGR  
RRPGRGLPTGGGGLAAAAGREVAQGLCDAIRLDGGDLRLRLQAPELETRVQAARL  
LEQILVAENRDRVARIGLGVILNLAKEREPVELARSVAGILEHMFKHSEETCQRLVAAGG  
LDAVLYWCRRTDPALLRHCALALGNALHGGQAVQRRMVEKRAAEWLFPLAFSKEDE  
LLRLHACLAVAVLATNKEVEREVERSGTLALVEPLVASLDPGRFARCLVDASDTSQGRG  
PDDLQRLVPLLDNRLEAQCIGAFYLCAEAAIKSLQGKTKVFSDIGAIQSLKRLVSYSTNG  
TKSALAKRALRLLGEEVPRPILPSVPSWKEAEVQTLQQIGFSKYCESFREQQVDGDL  
LRLTEEELQTDLG MKSGITRKRFFRELTELKTFANYSTCDRSNLADWLGS LDPRFRQYT  
YGLVSCGLDRSLLHRVSEQQLLED CGIHLGVHRARILTAAREMLHSPLPCTGGKPSGDT  
PDVFISYRRNSGSQLASLLKVHLQLHGFSVFIDVEKLEAGKFEDKLIQSVMGARNFVLVL  
SPGALDKCMQDHDCKDWVHKEIVTALSCGKNIVPIIDGFEWPEPQVLPEDMQAVLT FN  
GIKWSHEYQEATIEKIIRFLQGRSSRDSSAGSDTSLEGAAPMGPT

SEQ ID No: 29

MSGELPPNINIKEPRWDQSTFIGRANHFFT VTDPRNILLTNEQLESARKIVHDYRQGIVP  
PGLTENELWRAKYIYDSAFHPDTGEKMILIGRMSAQVPMNMTITGCMMTFYRTTPAVLF  
WQWINQSFNNAVNYTNRSGDAPLTVNELGTAYVSATTGAVATALGLNALTKHVSPLIGR



FVPFAAVAAANCINIPLMRQRELKVGIPVTDENG NRLGESANA AKQAITQVVVSRILMAA  
PGMAIPPFIMNTLEKKAFLKRFPWMSAPIQVGLVGFCLVFATPLCCALFPQKSSMSVTSL  
EAELQAKIQESHPELRRVYFNKGL

SEQ ID No: 30

MATRSSRRESRLPFLFTLVALLPPGALCEVWTQRLHGGSA PLPQDRGFLVVQGDPREL  
RLWARGDARGASRADEKPLRRKRSAALQPEPIKVY GQVSLNDSHNQM VVHWAGEKS  
NVIVALARDSLALARP KSSDVYVS YDYGKSFKKISDKLNFGLGNRSEAVIAQFYHSPADN  
KRYIFADAYAQYLWITFDFCNTLQGFSIPFRAADLLLH SKASNLLLG FDRSHPNKQLWKS  
DDFGQTWIMIQEHVKSFSWGIDPYDKPNTIYIERHEPSGYSTVFRST DFFQSRENQEVIL  
EEVRDFQLRDKYMFATKV VHLLGSEQQSSVQLWVSFGRKPMRAAQFVTRHPINEYYIA  
DASEDQVFVCVSHSNNRTNLYISEA EGLKFSLSENVLYYSPGGAGSDTLVRYFANE PF  
ADFHRVEGLQGVYIATLINGSMNEENMRSVITFDKGGTWEFLQAP AFTGYGEKINCELS  
QGCSLHLAQRLS QLLNLQLRRMPILSKESAPGLIATG SVGKNLASKTNVYISSSAGARW  
REALPGPHYYTWGDHGGIITAIAQGMETNELKYSTNEGETWKTFIFSEKPVFVYGLLTEP  
GEKSTVFTIFGSNKENVH SWLILQVNATDALGVPCTENDYKLWSPSDERGNECLLGHK  
TVFKRRTPHATCFNGEDFDRPVVVSNC SCTREDYECDFGFKMSEDLSLEV CVPDPPEFS  
GKSYSPPVPCPVG STYRRTRGYRKISGDTCSGGDVEARLEGE LVPCPLAEENE FILYAV  
RKSIYRYDLASGATEQLPLTGLRAAVALDFDYEHNCLYWSDLALDVIQRLCLNGSTGQE  
VIINSGLETVEALAFEPLSQLLYWVDAGFKKIEVANPDGDFRLTIVNSSVLDRPRALVLVP  
QEGVMFWTDWGD LKPGIYRSNMDGSAAYHLVSE DVKWPNGISVDDQWIYWTDAYLE  
CIERITFSGQQRSVILDNLPHPYAIAVFKNEIYWDDWSQLSIFRASKYSGSQMEILANQLT  
GLMDMKIFYKGKNTGSNACVPRPCSLLCLPKANN SRSCRCPEDVSSSVLP SGDL MCD  
CPQGYQLKNNTCVKEENTCLRNQYRCSNGNCINSIWWCDFDND CGDMSDERNCPTTI  
CDLDTQFRCQESGTCIPLSYKCDLEDDCGDNSDESHCEMHQCRSDEYNCSSGMCIRS  
SWVCDGDND CRDWSDEANCTAIYHTCEASN FQCRNGHCIPQRWACDGD TDCQDGS  
DEDPVNCEKKCNGFRCPNGTCIPSSKHCDGLRDCSDGSDEQHCEPLCTHFMD FVCKN  
RQQCLFHSMVCDGIIQCRDGSDEDAAFAGCSQDPEFHKVCDEF GFQCQNGVCISLIWK  
CDGMDDCGDYSDEANCENPTEAPNCSRYFQFRCENGHCIPNRWKCDREND CGDWS  
DEKDCGDSHILPFSTPGPSTCLPNYYRCSSGTCVMDTWVCDGYRDCADGSDEEACPL  
LANVTAASTPTQLGRCDRFEFECHQPKTCIPNWKRC DGHQDCQDGRDEANCPTHSTL  
TCMSREFQCEDGEACIVLSERCDGFLDCSDESDEKACSD ELTVYKVQNLQWTADFSG  
DVTLTWMRPKKMPSASC VYNVYYRVVGESIWK TLETHSNKTN TVLKVLKPD TTYQVKV  
QVQCLSKAHNTNDFVTLRTPEGLPDAPRN LQLSLPREAEGVIVGHWAPPIH THGLIREYI

VEYSRSGSKMWASQRAASNFTIKNLLVNTLYTVRVA AVTSRGIGNWSDSKSITTIGK  
 VIPPPDIHIDSYGENYLSFTLTME SDIKVNGYVVNLFWAFDTHKQERRTLNFRGSILSHKV  
 GNLT AHTSYEISAWAKTDLGDSPLAFEHVMTRGVRPPAPSLKAKAINQTAVECTWTGP  
 RNVVYGIFYATSFLDLYRNP KSLTTS LHNKTVIVSKDEQYLFLVRVVVPYQGPSSDYVVV  
 KMIPDSRLPPRHLHVHTGKTSVVIKWESPYDSPDQDLLYAI AVKDLIRKTDRSYKVKS  
 NSTVEYTLN KLEPGGKYHIIVQLGNMSKDSSIKITTVSLSAPDALKIITENDHVLLFWKSLA  
 LKEKHFNESRGYEIHMFD SAMNITAYLGNTTDNFFKISNLKMGHNYTFTVQARCLFGNQI  
 CGEPAILLYDELGSGADASATQAARSTDVA AVVVPILFLILLSLGVGFAILYTKHRRQLSS  
 FTAFANSHYSSRLGSAIFSSGDDLGEDDEDAPMITGFSDDVPMVIA

SEQ ID No: 31

MLSLDFLDDVRRMNKRQLYYQVLNFGMIVSSALMIWKGLMVITGSESPIVVVLSGSMEP  
 AFHRGDLLFLTNRVEDPIRVGEIVVFRIEGREIPIVHRVLKIHEKQNGHIKFLT KGDNNAVD  
 DRGLYKQGQHWLEKKDVVGRARGFVPYIGIVTILMNDYPKFKYAVLFLLGLFVLVHRE

SEQ ID No: 32

MNTVLSRANSLFAFSLSVMAALTFGCFITTA FKDRSVPVRLHVSRIMLKNVEDFTGPRER  
 SDLG FITSDITADLENIFDWNVKQLFLYLSAEYSTKNNALNQVVLWDKIVLRGDNPKLLLK  
 DMKTKYFFFDDGNGLKGNRNVTLT LSWNVVPNAGILPLVTGSGHVSVPFPD TYEITKSY

SEQ ID No: 33

MAAAAVQGGRRSGGSGGCSGAGGASNCGTGSGRSGLLDKWKIDDKPVKIDKWDGSAV  
 KNSLDDSAKKVLLEKYKYVENFGLIDGRLTICTISCF FAIVALIWDYMHPPESKPV LALC  
 VISYPLFMLS FVMMGILTIYTSYKEKSIFLVAHRKDPTGMDPDDIWQLSSSLKRFD DKYTL  
 KLTFISGR TKQQREAEFTKSI AKFFDHSGTLVMDAYEPEISRLHDSLAIERKIK

SEQ ID No: 34

MRPEPGGCCCRRTVRANGCVANGEVRNGYVRSSAAAAAAAAAAGQIHHVTQNGGLYK  
 RPFNEAFEETPMLVAVLTYVGYGVLT LFGYLRDFLRYWRIEKCHHATEREEQKDFVSLY  
 QDFENFYTRNLYMRIRDNWNRPICSVPGARVDIMERQSHDYNWSFKYTGNIIKGVINMG  
 SYN YLG FARNTGSCQEAAAKVLEEY GAGVCSTRQEIGNLDKHEELEELVARFLGVEAA  
 MAYGMGFATNSMNIPALVGKGCLILSDELN HASLV LGARLSGATIRIFKHNNMQSLEKLL  
 KDAIVYGQPRTRRPWKKILILVEGIYSMEGSIVRLPEVIALKKKYKAYLYLDEAHSIGALGP  
 TGRGVVEYFGLDPEDVDVMMGTFTKSF GASGGYIGGKKELIDYLRTHSHSAVYATSLS

PPVVEQIITSMKCMGQDGTSLGKECVQQLAENTRYFRRRLKEMGFIIYGNE DSPVVPL  
MLYMPAKIGAFGREMLKRNIGVVVVGF PATPIIESRARFCLSA AHTKEILD TALKEIDEVG  
DLLQLKYSRHRLVPLLD RPFDETTYEETED

SEQ ID No: 35

MPAHL LQDDISSSYTTTTTITAPPSRVLQNGGDKLETMPLYLEDDIRPD IKDDIYDPTYKD  
KEGPSPKVEYVWRNIILMSLLHLGALYGITLIPTCKFYTWLWGVFYYFVSALGITAGAHRL  
WSHRSYKARLPLRLFLIIANTMAFQNDVYEW ARDHRAHHKFSETHADPHNSRRGFFFS  
HVGWLLVRKHPAVKEKGSTLDLSDLEAEKLV MFQRRYYKPGLLMMCFILPTLVPWYFW  
GETFQNSVFVATFLRYAVVLNATWL VNSAAHLFGYRPYDKNISPRENILVSLGAVGEGF  
HNYHHSFPYDYSASEYRWHINFTTFFIDCMAALGLAYDRKKVSKAAILARIKRTGDGNYK  
SG

SEQ ID No: 36

MSGLSGPPARRGPFPLALLLLFLLGPRLVL AISFHLPINSRKCLREEIHKDLLVTGAYEISD  
QSGGAGGLRSHLKITDSAGHILYSKEDATKGKFAFTTEDYDMFEVCFESKGTGRIPDQL  
VILDMKHGVEAKNYEEIAKVEKLPLEVELRRLEDLSESIVNDFAYMKKREEEMRDTNES  
TNTRVLYFSIFSMFCLIGLATWQVFYLR RFFKAKKLIE

SEQ ID No: 37

MSGCGLFLRTTAAARACRGLVVSTANRRLLRTSPPVRAFAKELFLGKIKKKEVFPPFEV  
SQDELNEINQFLGPVEKFFTEEVD SRKIDQEGKIPDETLEKLKSLGLFGLQVP EEEYGGGLG  
FSNTMYSRLGEIISMDGSITVTLAAHQ AIGLKGIILAGTEEQKAKYLPKLASGEHIAAFCLT  
EPASGSDAASIRSRATLSEDKKH YILNGSKVWITNGGLANIFTVFAKTEVVDS DGSVKDK  
ITAFIVERDFGGVTNGKPEDKLGIRGSNTCEVHFENTKIPVENILGEVGDGFKVAMN ILNS  
GRFSMGSVVAGLLKRLIEMTA EYACTRKQFNKRLSEFGLIQEKFALMAQKAYVMESMT  
YLTAGMLDQPGFPDCSIEAAMVKVFSSEA AWQCVSEVLQILGGLGYTRDYPYERILRDT  
RILLIFEGTNEILRMYIALTGLQHAGRILTTRIHELKQAKVSTVMDTVGRRLRDSLGR TVDL  
GLTGNHGVVHPSLADSANKFEENTYCFGR TVETLLLRF GKTIMEEQLV LKRVANILINLY  
GMTAVLSRASRSIRIGLRNHDHEVLLANTFCVEAYLQNLFSLSQLDKYAPENLDEQIKKV  
SQQILEKRAYICAHPLDRTC

SEQ ID No: 38

MFSLSSTVQPQVTVPLSHLINAFTPKNTSVSLSGVSVSQNQHRDVVPEHEAPSSEPSL  
NLRDLGLSELKIGQIDQLVENLLPGFCKGKNISHWHTSHVSAQSFFENKYGNLDIFSTL  
RSSCLYRHHSRALQSICSDLQYWPVFIQSRGFKTLKSRTTRRLQSTSERLAETQNIAPSF  
VKGFLLRDRGSDVESLDKLMKTKNIPEAHQDAFKTGFAEGFLKAQALTQKTNDLSLRRT  
LILFVLLLFGIYGLLKNPFLSVRFRTTTGLDSAVIDPVQMKNVTFEHVKGVEEAKQELQEV  
VEFLKNPQKFTILGGKLPKGILLVGPPGTGKTLLARAVAGEADVPFYYASGSEFDEMFB  
GVGASRIRNLFREAKANAPCVIFIDELDSVGGKRIESPMHPYSRQTINQLLAEMDGFKPN  
EGVIIIIGATNFPEALDNALIRPGRFDMQVTVPRPDVKGRTEILKWYLNKIKFDQSVDP  
RGTVGFGSGAELENLVNQAALKAASVDGKEMVTMKELEFSKDKILMGPERRSVEIDNKNK  
TITAYHESGHAIAYYTKDAMPINKATIMPRGPTLGHVSLLPENDRWNETRAQLLAQMDV  
SMGGRVAEELIFGTDHITTGASSDFDNATKIAKRMVTKFGMSEKLGVM TYSDTGKLSPE  
TQSAIEQEIRILLRDSYERAKHILKTHAKEHKNLAEALLTYETLDAKEIQIVLEGKKLEVR

SEQ ID No: 39

MSVPSSLSQSAINANSHGGPALSPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGEGG  
GPEPGPANAKWLKEGQNQLRRAATAHRDQNRNVTLTAAEEASQEPEMAPLGPKGLIHL  
YSELELSAHNAANRGLRGPGLIISTQEQQPDEGEKEAAGEAEEEEEDDDDEEEEEEDLS  
SPPGLPEPLESVEAPPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
SYGSPEDTDSFWNPNAFETDSDL PAGWMRVQDTSGTYYYWHIPTGTTQWEPPGRASP  
SQGSSPQEESQLTWTGFAHGEGFEDGEFWKDEPSDEAPMELGLKEPEEGTLTFPAQS  
LSPEPLPQEEEEKLPPRNTNPGIKCFAVRSLGWVEMTEEELAPGRSSVAVNNCIRQLSYH  
KNNLHDPMSGGWGEGKDLLLQLEDETLLKLV EPQSQALLHAQPIISIRVWGVGRDSGRD  
FAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICSKARPPPLPGLIMAERRNARCLVN  
GLSLDHSKLVDPVFQVEFPAPKNELVQKFQVYYLGNVPVAKPVGVVDVINGALESVLSSS  
SREQWTPSHVSVAPATLTILHQQTEAVLGECRVRFLSFLAVGRDVHTFAFIMAAGPASF  
CCHMFWCEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWT  
VRRGVQSLWGSLLKPKRLGAHTP

SEQ ID No: 40

RHTRTHRDTRHTYTHAHTDAHTCTHMHRDTQMHTHTICRKKYALTNIAAMGLSDPAA  
QPLLGNGSANIKLVKNGENQLRKAAEQGQQDPNKNLSPTAVINITSEKLEGKEPHQDS  
SSCEILPSQPRRTKSFLNYYADLETSAELEQNRGNHHGTAEKESQPVQGGQASTIING  
DLLLQKPNRPQSSPEDGQVATVSSSPETKKDHPKTGAKTDCALHRIQNLA PSDEESSW  
TTLSQDSASPSSPDETDIWSDFSQTDPDLP PGWKRVSDIAGTYYYWHIPTGTTQWERP



VSIPADLQGSRKGSLSVTPSPTPENЕКQPWSDFAVLNГGKINSДИWKDLHAATVNPDP  
SLKEFEGATLRYASLKLRNAPHPPDDDDSCSINSДPEAKCFAVRSLGWVEMAEEDLAPG  
KSSVAVNNCIRQLSYCKNDIRDТVGIWGEGKDMYLILENDMLSLVDPMDRSVWHSQPIV  
SIRVWGVGRDNGRDFAYVARDKDTRILKCHVFRCDTPAKAIATSLHEICKIMAERKNAK  
ALACSSLQERANVNLDVPLQVDFTPКTELVQKFHVQYLGMLPVDPKPVGMDILNSAIEN  
LMTSSNKEDWLSVNMNVADATVTVISEKNEEEVLVECRVRFLSFMGVGKDVHTFAFIM  
DTGNQRFЕCHVFWCEPNAGNVSEAVQAACMLRYQKCLVARPPSQKVRPPPPPADSV  
TRRVTTNVKRGVLSLIDTLKQKRPVTEMP

SEQ ID No: 41

MAFVCLAIGCLYTFLISTTFGCTSSSDTEIKVNPPQDFEIVDPGYLGYLYLQWQPPLSLD  
HFKECTVEYELKYRNIGSETWKTITKNLHYKDGFDLNKGIEAKIHTLLPWQCTNGSEVQ  
SSWAETTYWISPQGIPETKVQDMDCVYYNWQYLLCSWKPGIGVLLDTNYNLFYWYEG  
L  
DHALQCVDYIKADGQNIGCRFPYLEASDYKDFYICVNGSSSENKPIRSSYFTFQLQNIVKP  
LPPVYLTFTRESSCEIKLKWSIPLGPIPARCFDYEIEIREDDTTLVТATVENETYTLKTTNE  
TRQLCFVVRSKVNIYCSDDGIWSEWSDKQCWEGEDLSKKTLLRFWLPFGFILILVIFVTG  
LLLRKPNTYPKMIPEFFCDT

SEQ ID No: 42

MVNYAWAGRSQRKLWWRSVAVLTCKSVVRPGYRGGLQARRSTLLKTCARARATAPG  
AMKMVAPWTRFYNSCCLCCHVRTGTILLGVWYLIINAVVLLILLSALADPDQYNFSSE  
LGGDFEFMDDANMCIAIAISLLMILICAMATYGAYKQRAAWIIPFFCYQIFDFALNMLVAIT  
VLIYPNSIQEYIRQLPPNFPYRDDVMSVNPTCLVLIILLFISIILTFKGYLISCVWNCYRYING  
RNSSDVLVYVTSNDTTVLLPPYDDATVNGAAKEPPPPYVSA

SEQ ID No: 43

MGSELETAMETLINVFHAHSGKEGDKYKLSKKELKELLQTELSGFLDAQKDVDKVM  
KELDENGDGЕVDFQEYVVLVAALTVACNNFFWENS

SEQ ID No: 44

MSELEKAMVALIDVFHQYSGREGDKHKLKKSELKELINNELSHFLEEIKEQEVDKVMET  
LDNDGDGECDFFQEFMAFVAMVTTACHEFFEHE  
SEQUENCES OF THE INDIVIDUAL PROTEINS

SEQ ID No: 45

IATVIVITLVMLKKKQYTSIHGVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No: 46

MASALEQFVNSVRQLSAQGQMTQLCELINKSGELLAKNLSHLDTVLGALDVQEHSLGVL  
AVLFVKFSMPSPDFETLFSQVQLFISTCNGEHIRYATDTFAGLCHQLTNALVERKQPLR  
GIGILKQAIDKMQMNTNQLTSIHADLCQLCLLAKCFKPALPYLDVDMMDICKENGAYDAK  
HFLCYYYYGGMIYTGLKNFERALYFYEQAITTPAMAVSHIMLESYKKYILVSLILLGKVQQ  
LPKYTSQIVGRFIKPLSNAYHELAQVYSTNNPSELRNLVKNHSETFTRDNNMGLVKQCL  
SSLYKKNIQRLTKTFLTLSLQDMASRVQLSGPQEAKEYVLHMIEDGEIFASINQKDGMVS  
FHDNPEKYNNPAMLHNIDQEMLKCIELDERLKAMDQEITVNPQFVQKSMGSQEDDSGN  
KPSSYS

SEQ ID No: 47

MSNLSKGTGSRKDTKMRIRAFPMTMDEKYVNSIWDLLKNAIQEIQRKNNSGLSFEELYR  
NAYTMVLHKHGEKLYTGLREVVTEHLINKVREDVLNSLNNNFLQTLNQAWNDHQTAMV  
MIRDILMYMDRVYVQQNNVENVYNLGLIIFRDQVVRYGCIRDHLRQTLDDMIARERKGEV  
VDRGAIRNACQMLMILGLEGRSVYEEDFEAPFLEMSAEFFQMESQKFLAENSASVYIKK  
VEARINEEIERVMHCLDKSTEEPIVKVVERELISKHMKTIVEMENSGLVHMLKNGKTEDL  
GCMYKLFSRVPNGLKTMCECMSSYLREQGKALVSEEGEGKNPVDYIQGLLDLKSFRDR  
FLLESFNNDRLFQTIAGDFEYFLNLNSRSPEYLSLFIDDKLKKGVKGLTEQEVETILDKA  
MVLFRFMQEKDVFERYYKQHLARRLLTNKSVSDDSEKNMISKLKTECGCQFTSKLEGM  
FRDMSISNTTMDEFQRHLQATGVSLGGVDLTVRVLTGTYWPTQSATPKCNIPPAPRHA  
FEIFRRFYLAHSGRQLTLQHMHMGSADLNATFYGPVKKEDGSEVGVGGAQVTGSNTRK  
HILQVSTFQMTILMLFNNREKYTFEEIQQETDIPERELVRALQSLACGKPTQRVLTKEPK  
SKEIENGHIFTVNDQFTSKLHRVKIQTVAAKQGESDPERKETRQKVDDDRKHEIEAAIVRI  
MKSRKKMQHNVLVAEVTQQLKARFLPSPVVIKKRIEGLIEREYLARTPEDRKVYTYVA

SEQ ID No: 48

MLRRVTVAAVCATRRKLCEAGRELAALWGIETRGRCEDSAAARPPILAMPGRNKAKS  
TCSCPDLQPNGQDLGENSRVARLGADESEEEGRRGSLSNAGDPEIVKSPSPDKQYRYI  
KLQNGLQALLISDLSNMEGKTGNTTDDDEEEEEVEEEEEDDDDEDSGAEIEDDDEEGFDDE  
DEFDDEHDDDLDTEDNELEEELEERAERARKKTTEKQSAAALCVGVGSFADPDDLPLGLAH  
FLEHMFVFMGSLKYPDENGFDAFLKKHGGSDNASTDCERTVFQFDVQRKYFKEALDRW

AQFFIHPLMIRDAIDREVEAVDSEYQLARPSDANRKEMLFGSLARPGHPMGKFFWGNA  
ETLKHEPRKNNIDTHARLREFWMRYSSHYMTLVVQSKETLDTLEKWVTEIFSQIPNNG  
LPRPNFGHLTDPFDTPAFNKLYRVVPIRKIHALTITWALPPQQQHRYVKPLHYISWLVGH  
EGKGSILSFLRKKCWALALFGGNGETGFEQNSTYSVFSISITLTDEGYEHFYEVAYTVFQ  
YKMLQKLGPEKRIFEEIRKIEDNEFHYYEQETDPVEYVENMCENMQLYPLQDILTGDQLL  
FEYKPEVIGEALNQLVPQKANLVLLSGANEGKCDLKEKWFGTQYSIEDIENSWGELWNS  
NFELNPDHLPAENKYIATDFTLKAFCPETEYPVKIVNTPQGCLWYKKDNKFKIPKAYIR  
FHLISPLIQKSAANVVLFDIFVNILTHNLAEPAYEADVAQLEYKLVAGEHGLIIRVKGFNHNK  
LPLLFQLIIDYLAEFNSTPAVFTMITEQLKKTYFNILIKPETLAKDVRLLEIYARWSMIDKY  
QALMDGLSLESLLSFVKEFKSQLFVEGLVQGNVTSTESMDFLKYVVDKLNFKPLEQEMP  
VQFQVVELPSGHHLCKVKALNKG DANSEVTVYYQSGTRSLREYTLMELLVMHMEEP  
CFDFLRTKQTLGYHVYPTCRNTSGILGFSVTVGTAQTKYNSEVVDKKIEEFLSSFEK  
KIENL TEEAFNTQVTALIKLKECEDTHLGEEVDRNWNNEVVTQQYLFDR  
LAHEIEALKSFSKSDLV NWFKAHRGPGSKMLSVH  
AVGYGKYELEEDGTPSSEDSNSSCEVMQLTYLPTSPLLAS  
VSSPLLISGLSQQHSTFSPTIK

SEQ ID No: 49

MGKQNSKLAPVEMEDLVKSTEFNEHELKQWYKGFLKDCPSGRLNLEEFQQLYVKFFPY  
GDASKFAQHAFRTFDKNGDGTIDFREFICALSITSRGSFEQKLNWAFNMYDLDDGDKIT  
RVEMLEIIIEAIYKMVGTVIMMKMNEDGLTPEQRVDKIFSKMDKNKDDQITLDEFKEAAKS  
DPSIVLLLQCDIQK

SEQ ID No: 50

MLGGSGSHGRRSLAALSQIAYQRNDDDEEEAARERRRRRARQERLRQKQEEESLGQVT  
DQVEVNAQNSVPDEEAKTTTTNTQVEGDDEAAFLERLARREERRQKRLQEALERQKEF  
DPTITDASLSLPSRRMQNDTAENETTEKEEKSESQRQERYEIEETETVTKSYQKNDWRDA  
EENKKEDKEKEEEEEEEKPKRGSIGENQIKDEKIKKDKEPKKEEVKSFMDRKKGFTEVKSQ  
NGEFMTHKLKHTENTFSRPGGRASVDTKEAEGAPQVEAGKRLEELRRRRRGETESEEF  
EKLKQKQQEAAL EELKKKREERRKVLEEEEEQRRKQEEADRKLREEEEEKRRLKEEIER  
RRAEAAEKRQKMPEDGLSDDKKPFKCFTPKGSSLKIEERAFLNKS  
VQKSSGVKSTHQ AAIVSKIDSRLEQYTS  
AIEGTKSAKPTKPAASDLPVPAEGVRNIKSMWEKGNVFSSPTAA  
GTPNKETAGLKVGVS  
SRINEWLTKTPDGNKSPAPKPSDLRPGDVSSKRNLWEKQSVD  
KVTSP TKV

SEQ ID No: 51

MSEHVEPAAPGPGPNGGGGGGPAPARGPRTPNLNPINVRDRLFHALFFKMAVTYS  
RLFPPAFRRRLFEEFVLLKALFVLFVLAYIHIVFSRSPINCLEHVRDKWPREGILRVEVRHN  
SSRAPVFLQFCDSGGGRGSFPGLAVEPGSNLDMEDEEEEEELTMEMFGNSSIKFELDIEP  
KVFKPPSSSTEALNDSQEFPFPETPTKVWPQDEYIVEYSLEYGFLRLSQATRQRLSIPVM  
VVTLDPTRDQCFGDRFSRLLLDEFLGYDDILMSSVKGLAENEENKGFLRNVVSGEHYRF  
VSMWMARTSYLAFAIMVIFTLSVSMMLRYSHHQIFVFIVDLLQMLEMNMAIAFPAAPLLT  
VILALVGMEAIMSEFFNDTTTAFYIILIVWLADQYDAICCHTSTSKRHWLRFFFYLYHFAFYA  
YHYRFNGQYSSLALVTSWLFIQHSMIYFFHHYELPAILQQVRIQEMLLQAPPLGPGTPTA  
LPDDMNNNSGAPATAPDSAGQPPALGPVFELVSKERGWGSAEGSGGVLVGLQ

SEQ ID No: 52

MDTSRLGVLLSLPVLLQLATGGSSPRSGVLLRGCPHCHCEPDGRMLLRVDCSDLGLS  
ELPSNLSVFTSYLDLSMNNISQLLPNPLPSLRFLEELRLAGNALTYPKGAFGLYSLKVL  
MLQNNQLRHVPTEALQNLRLSLQSLRLDANHISYVPPSCFSGLHSLRHLWLDDNALTEIP  
VQAFRSLSALQAMTLALNKIHHIPDYAFGNLSSLVVLHLHNNRIHSLGKKCFDGLHSLET  
LDLNYNNLDEFPTAIRTLNLKELGFHSNNIRSIPEKAFVGNPSLITIHFYDNPIQFVGRSA  
FQHLPELRTLTLNGASQITEFPDLTG TANLESLTLTGAQISSLPQTVCNQLPNLQVLDLSY  
NLLEDLPSFSVCQKLQKIDLRHNEIYEIKVDTFQQLLSLRSLNLAWNKAIIHPNAFSTLPS  
LIKLDLSSNLLSSFPITGLHGLTHLKLGTGNHALQSLISSENFPELKVIEMPYAYQCCAFGV  
CENAYKISNQWNKGDNSSMDDLHKKDAGMFQAQDERDLEDFLDFFEDLKALHSVQC  
SPSPGPFKPCHELLDGWLIRIGVWTIAVLALTCNALVTSTVFRSPLYISPIKLLIGVIAAVN  
MLTGVSSAVLAGVDAFTFGSFARHGAWWENGVGCHVIGFLSIFASESSVFLTLAALER  
GFSVKYSAKFETKAPFSSLKVIILLCALLALTMAAVPLLGGSKYGASPLCLPLPFGEPSTM  
GYMVALILLNSLCFLMMTIAYTKLYCNLDKGDLENIWDCSMVKHIALLLFTNCILNCPVAF  
LSFSSLINLTFISPEVIKIFILLVVVPLPACLNPLLYILFNPHFKEDLVSLRKQTYVWTRSKHP  
SLMSINSDDVEKQSCDSTQALVTFTSSSITYDLPPSSVPSPAYPVTESCHLSSVAFVPCL

SEQ ID No: 53

KEQSELDQDLDDVEEVEEEEETGEETKLKARQLTVQMMQNPQILAALQERLDGLVETPT  
GYIESLPRVVKRRVNALKNLQVKCAQIEAKFYEEVHDLERKYAVLYQPLFDKRFEIINAIY  
EPTEEECWKPDEEDEISEELKEKAKIEDEKKDEEKEDPKGIPEFWLTVFKNVDLLSDM  
VQEHDEPILKHLKDIKVKFSDAGQPMSFVLEFHFEPNEYFTNEVLTKTYRMRSEPDDSD  
PFSFDGPEIMGCTGCQIDWKKGKNVTLKTIKKKQKHKGRTVRTVTKTVSNDSEFFNFFA



PPEVIPKFSADFDDAEAILAADFEIGHFLRERIIPRSVLYFTGEAIEDDDDDYDEEGEEAD  
EGYQLFEEVKSCSKLFQRWLQ

SEQ ID No: 54

MAQALPWLLLWMGAGVLP AHGTQH GIRLPLRSG LGGAPLGLRLPRETDEEPEEPGRR  
GSFVEMVDNLRGKSGQGYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHPFLHRYYQ  
RQLSSTYRDLRKGVYVPYTQGKWE GELGTDLLCGAGFPLNQSEVLASVGGSMIIGGID  
HSLYTGSLWYTPIRREWYYEVIIVRVEINGQDLKMDCKEYNYDKSIVDSGTTNLRLPKKV  
FEAAVKSIIKAASSTEKFPDGFWLGEQLVCWQAGTTPWNIFPVISLYLMGEVTNQSFRTI  
LPQQYL RPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRARKRIGFAVSAC  
HVVHDEFRTAAVEGPFVTLDMEDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQ  
WRCLRCLRQQHDDFADDISLLK

SEQ ID No: 55

MAATGTAAAAATGRLLLLLLVGLTAPALALAGYIEALAANAGTGFAVAEPQIAMFCGKLN  
MHVNIQTGKWE PDPTG TKSCFETKEEVLQYCQEMYPELQITNVMEANQRVSIDNWCR  
RDKKQCKSRFVTPFKCLVGEFVSDVLLVPEKCQFFHKERMEVCENHQHWHTVVKEAC  
LTQGMTLYSYGM L L P C G V D Q F H G T E Y V C C P Q T K I I G S V S K E E E E E D E E E E E E D E E E D  
YDVYKSEFPTEADLED FTEAAVDEDEDEDEEEGEEVVEDRDYYYDTFKGDDYNEENPTE  
PGSDGTMSDKEITHDV KAVCSQEAMTGPCRAVM PRWYFDLSKGKCVRFIYGGCGGNR  
NNFESEDYCM AVCKAMIPPTPLPTNDVDVYFETSADDNEHARFQKAKEQLEIRHRNRM  
DRVKKEWEEAELQAKNLPKAERQTLIQHFQAMVKALEKEAASEKQQLVETHLARVEAM  
LNDRRRMALENYLAALQSDPPRPHRILQALRRYVRAENKDR LHTIRHYQHVLAVDPEKA  
AQMKSQVMTHLHVIEERRNQSLSLLYKVPYVAQEIQEEIDELLQEQRADMDQFTASISE  
TPVDVRVSSEEESEEIPPFHPFHPFPALPENEDTQPELYHPMKKGSGVGEQDGGGLIGAE  
EKVINSKNKVDENMVIDETLDVKEMIFNAERVGGLEEEERESVGPLREDFSLSSSALIGLL  
VIAVAIATVIVISLVMLRKRQYGTISHGIVEVDPMLTPEERHLNKMQNHGYENPTYKYLEQ  
MQI

SEQ ID No: 56

MRSPATGVPLPTPPPLLLLLLLLLLPPPLLGDQVGPCRS LGSRGRGSSGACAPMGWLC  
PSSASNLWLYTSRCRDAGTELTGHLVPHHDGLRVWCPESEAHIPPLPAPEGCPWSCR  
LLGIGGHLSPQGKLTLP E E H P C L K A P R L R C Q S C K L A Q A P G L R A G E R S P E E S L G G R R K R  
NVNTAPQFQPPSYQATVPENQPAGTPVASLRAIDPDEGEAGRLEYTMDALFDSRSNQF

FSLDPVTGAVTTAEELDRETKSTHVFRVTAQDHGMPRRSALATLTILVTDNDHDPVFE  
 QQEYKESLRENLEVGYEVLTVRATDGDAPPNANILYRLLEGSGGSPSEVFEIDPRSGVI  
 RTRGPVDREEVESYQLTVEASDQGRDPGPRSTTA AVFLSVEDDNDNAPQFSEKRYVV.  
 QVREDVTPGAPVLRVTASDRDKGSNAVHYSIMSGNARGQFYLDAQTGALDVVSPLDY  
 ETTKEYTLRVRAQDGGRPPLSNVSGGLVTVQVLDINDNAPIFVSTPFQATVLESVPLGYLV  
 LHVQAIDADAGDNARLEYRLAGVGHDFFPTINNGTGWISVAAELDREEVDFYSFGVEAR  
 DHGTPALTASASVSVTVLDVNDNNPTFTQPEYTVRLNEDAAVGTSVVTVSAVDRDAHS  
 VITYQITSGNTRNRFSITSQSGGGLVSLALPLDYKLERQYVLAVTASDGTRQDTAQIVVN  
 VTDANTHRPVFQSSHYTVNVNEDRPAGTTVVLISATDEDTGENARITYFMEDSIPQFRID  
 ADTGAVTTQAELDYEDQVSYTLAITARDNGIPQKSDTTYLEILVNDVNDNAPQFLRDSYQ  
 GSVYEDVPPFTSVLQISATDRDSGLNGRVFYTFQGGDDGDGDFIVESTSGIVRTLRRLD  
 RENVAQYVLRAYAVDKGMPPARTPMEVTVTVLDVNDNPPVFEQDEFDVFVEENSPIGL  
 AVARVTATDPDEGTNAQIMYQIVEGNIPEVFQLDIFSGELTALVDLDYEDRPEYVLVIQAT  
 SAPLVS RATVHVRLDRNDNPPVLGNFEILFNNYVTNRSSSFPGGAIGRVP AHDPDISD  
 SLTYSFERGNELSLVLLNASTGELKLSRALDNNRPLEAIMSVLVSDGVH SVTAQCALRVT  
 IITDEMLTHSITLRLEDMSPERFLSPLLGLFIQAVAATLATPPDHVVVFNVQRD TDAPGGH  
 ILNVSLSVGQPPGPGGGPPFLPSEDLQERLYLNRSLLTAISAQRVLPFDDNICLREPCEN  
 YMRCVSVLRFDSSAPFIASSSVLFRPIHPVGGLRCRCPPGFTGDYCETEVDLCYSRPCG  
 PHGRCRSREGGYTCLCRDGYTGEHCEVSARSGRCTPGVCKNGGTCVNLLVGGFKCD  
 CPSGDFEKPYPYCQVTTRSFP AHSFITFRGLRQRFHFTLALS FATKERDGLLLYNGRFNEK  
 HDFVALEVIQEQVQLTFSAGESTTTVSPFVPGGVSDGQWHTVQLKYYNKPLL GQTGLP  
 QGPSEQKVAVVTVDGCDTGVALRFGSVLGNYSCAAQGTQGGGSKKSLDLTG PLLGGV  
 PDLPE SFPVRMRQFVGCMRNLQVDSRHIDMADFIANNGTVPGCPAKKNVCDSNTCHN  
 GGTCVNQWDAFSCECPLGFGGKSCAQEMANPQHFLGSSLVAWHGLSLPISQPWYLSL  
 MFRTRQADGVLLQAITRGRSTITLQLREGHVMLSVEGTGLQASSLRLEPGRANDGDWH  
 HAQLALGASGGPGHAILSFDYGGQRAEGNLGPRLHGLHLSNITVGGIPGPAGGVARGF  
 RGCLQGVRVSDTPEGVNSLDPSHGESINVEQGCSLPDPCDSNPCPANSYCSNDWDSY  
 SCSCDPGYYGDNCTNVCDLNPCEHQSVCTRKPSAPHGYTCECPPNYLGPYCETRIDQ  
 PCPRGWWGHPTCGPCNCDVSKGFDPCNKTSGECHCKENHYRPPGSPTCLLCD CYP  
 TGSLSRVCDPEDGQCPCPKPGVIGRQC DRCDNPFAEVT TNGCEVNYDSCPRAIEAGIW  
 WPRTRFGLPAAAPCPKGSFGTAVRH CDEHRGWLP PNLFNCTSITFSELKGFAERLQRN  
 ESGLD SGRSQQ LALLRNATQHTAGYFGSDVKVAYQLATRLLAHESTQRGFGLSATQD  
 VHFTENLLRVGSALLDTANKRHWELIQQTEGGTAWLLQH YEAYASALAQNMRHTYLSP  
 FTIVTPNIVISVVRLDKGNFAGAKLPRYEALRGEQPPDLETTVILPESVFRET PPVVRPAG

PGEAQEPEELARRQRRHPELSQGEAVASVIIYRTLGLPHNYDPDKRSLRVPKRPIINT  
PVVSISVHDDEELLPRALDKPVTQFRLLTEERTKPICVFWNHSILVSGTGGWSARGC  
EVVFRNESHVSCQCNHMTSFAVLMDVSRRENGEILPLKTLTYVALGVTLAALLTFFFLT  
LLRILRSNQHGIRRNLTAAALGLAQLVFLGGINQADLPFACTVIAILLHFLYLCTFSWALLEAL  
HLYRALTEVRDVNTGPMRFYYMLGWGVPFITGLAVGLDPEGYGNPDFCWLSIYDTLI  
WSFAGPVAFAVSMVFLYILAAASCAAQRQGFEEKGPVSGLQPSFAVLLLLSATWLLA  
LLSVNSDTLLFHLYLFATCNCIQGPFIFLSYVVLSKEVRKALKLACSRKPSPDPALTTKSTL  
TSSYNCPSPYADGRLYQPYGDSAGSLHSTSRSGKSQPSYIPFLLREESALNPGQGPPG  
LGDPGSLFLEGQDQQHDPDSDSDLSLEDDQSGSYASTHSSDSEEEEEEEEEEEAAAF  
PGEQGWDSLLGPGAERLPLHSTPKDGGPGPGKAPWPGDFGTAKESSGNGAPEERL  
RENGDALSREGSLGPLPGSSAQPHKGILKKKCLPTISEKSSLLRLPLEQCTGSSRGSSA  
SEGSRGGPPPRPPPRQSLQEQLNGVMPIAMSIKAGTVDEDSSGSEFLFFNFLH

SEQ ID No: 57

MGKGGNQGEAAREVSVPTFSWEEIQKHNLRTDRWLVIDRKVYNITKWSIQHPGGQ  
RVIGHYAGEDATDAFRAFHPDLEFVGKFLKPLLIGELAPEEPSQDHGKNSKITEDFRALR  
KTAEDMNLFKTNHVFFLLLLAHIIALESIAWFTVFYFGNGWIPTLITAFVLATSQAQAGWL  
QHDYGHLSVYRKPKWNHLVHKFVIGHLKGASANWWNHRHFQHHAKPNIFHKDPDVNM  
LHVFLGEWQPIEYGKKKLKYLPHNHQHEYFFLIGPPLLIPMYFQYQIIMTMIVHKNWVDL  
AWAVSYYIRFFITYIPFYGILGALLFLNFIRFLESHWFVWVTQMNHIVMEIDQEAYRDWFS  
SQLTATCNVEQSFFNDWFSGHLNFQIEHHLFPTMPRHNLHKIAPLVKSLCAKHGIEYQE  
KPLLRALLDIIRSLKKSGKLWLDAYLHK

SEQ ID No: 58

MEDLDQSPLVSSSDSPPRPQPAFKYQFVREPEDEEEEEEEEEDEDEDLEELEVLERT  
EFSELEYSEMGSFSVSPKAESAVIVANPREEIIVKNKDEEEKLVSNILHNQQELPTALT  
KLVKEDEVVSSEKAKDSFNEKRVAVEAPMREEYADFKPFERVWEVKDSKEDSDMLAA  
GGKIESNLESKVDKKCFADSLEQTNHEKDSESSNDDTSFPSTPEGIKDRSGAYITCAPF  
NPAATESIATNIFPLLGDPTSENKTDEKKIEEKKAQIVTEKNTSTKTSNPFLVAAQDSETD  
YVTTDNLTQVTEEVVANMPEGLTPDLVQEACESELNEVTGTKIAYETKMDLVQTSEVMQ  
ESLYPAAQLCPSFEESEATPSPVLPDIVMEAPLNSAVPSAGASVIQPSSSPLEASSVNYE  
SIKHEPENPPPYEEAMSVSLKKVSGIKEEIKEPENINAALQETEAPYISIACDLIKETKLSA  
EPAPDFSDYSEMAKVEQPVPDHSELVEDSSPDSEPVDLFSDDSIQDVPQKQDETVMQ  
KESLTETSFESMIEYENKEKLSALPPEGGKPYLESFKLSLDNTKDTLLPDEVSTLSKKEKI



PLQMEELSTAVYSNDDLFISKEAQIRETETFSDSSPIEIIDFPTLISSKTD SFSKLAREYT  
DLEVSHKSEIANAPDGAGSLPCTELPHDLSLKNIQPKVEEKISFSDDFSKNGSATSKVLL  
LPPDV SALATQAEIESIVKPKVLVKEAEKKLPSDTEKEDRSPSAIFSAELSKTSVVDLLYW  
RDIKKTGVVFGASLFLLLSLTVFSIVSVTAYIALALLSVTISFRIYKGVIAIQKSDEGHPFR  
AYLESEVAISEELVQKYSNSALGHVNCTIKELRRLFLVDDLVDLSLKFAVLMWVFTYVGAL  
FNGLTLLILALISLFSVPVIYERHQAQIDHYLGLANKNVKDAMAKIQAKIPGLKRKAE

SEQ ID No: 59

MAAETLLSSLLGLLLLGLLL PASLTGGVGSLNLEELSEMRYGIEILPLPVMGGQSQSSDV  
VIVSSKYKQRYECRLPAGAIHFQREREEETPAYQGPGIPELLSPMRDAPCLLKT KDWWT  
YEFCYGRHIQQYHMEDSEIKGEVLYLGYYSQAFDWDDDETAKASKQHRLKRYHSQTYG  
NGSKCDLNGRPREAEVRFLCDEGAGISGDYIDRVDEPLSCSYVLTIRTPRLCPHPLLRP  
PPSAAPQAILCHPSLQPEEY MAYVQRQAVDSKQYGDKIIEELQDLGPQVWSETKSGVA  
PQKMAGASPTKDDSKDSDFWKMLNEPEDQAPGGEEVPAEEQDPSPEAADSASGAPN  
DFQNNVQVKVIRSPADLIRFIEELKGGTKKGKPNIGQEQPVDDAAEVPQREPEKERGDP  
ERQREMEEEEEDEDEDEDEDEDERQLLGEFEKELEGILLPSDRDRLRSEVKAGMERELE  
NIIQEASPALPPTTEKELDPDGLKKESERDRAMLALTSTLNKLIKRL EEEKQSPELVKKHKKK  
RVVPKKPPSPQPTTEEDPEHRVRVRVTKLRLGGPNQDLTVLEMKREN PQLKQIEGLVK  
ELLEREGLTAAGKIEIKIVRPWAEGTEEGARWLTD E DTRNLKEIFFNILVPGAEEAQKER  
QRQKELESNYRRVWGSPGGEGTGDLDEFDF

SEQ ID No: 60

MRLPGAMPALALKGELLLL SLLLLLEPQISQGLVVTPPGPELV LNVSSSTFVLTCSGSAPV  
VWERMSQEPPQEMAKAQDGT FSSVLTLTNL TGLDTGEYFCTHND SRGLETDERKRLYI  
FVPDPTVGFLPNDAEELFIFLTEITEITIPCRVTD PQLVVTLHEKKGDVALPVPYDHQRGF  
SGIFEDRSYICKTTIGDREVDSDAYYVYRLQVSSINVS VNAVQTVVRQGENITLMCIVIGN  
EVVNFEW TYPRKEVIGRLVEPVTD FLLDMPYHIRSILHIPSAELED SGTYTCNVTESVND  
HQDEKAINITVVESGYVRLLGEVGTLQFAELHRSRTLQVVFEAYPPPTVLWFKDNRTL G  
DSSAGEIALSTRNVSETRYVSELTLVRVKVAEAGHYTMRAFHEDAEVQLSFQLQINVPV  
RVLELSESHPD SGEQTVRCRGRGMPQPNIWSACRDLKRCPRELPPTLLGNSSEEEESQ  
LETNVTYWEEEQEF EVVSTLRLQHVD RPLSVRCTLRNAVGQDTQE VIVVPHSLPFKVVV  
ISAILALVVLTIISLIILIMLWQKKPRYEIRWKVIESVSSDGHEYIYVDPMQLPYDSTWELPR  
DQLVLGRTL GSGAFGQVVEATAHGLSHSQATMKVAVKMLKSTAR SSEKQALMSELKIM  
SHLGPHLNVVNLLGACTKGGPIYIITEYCRYGDLVDYLHRNKHTFLQHHS DKRRPPSAEL



YSNALPVGLPLPSHVSLTGESDGGYMDMSKDESVDYVPMLDMKGDVKYADIESSNYM  
APYDNYVPSAPERTCRATLINESPVLSYMDLVGFSYQVANGMEFLASKNCVHRDLAAR  
NVLICEGKLVKICDFGLARDIMRDSNYISKGSTFLPLKWMAPESIFNSLYTTLSDVWSFGI  
LLWEIFTLGGTPYPELPMNEQFYNAIKRGYRMAQPAHASDEIYEIMQKCWEEKFEIRPP  
FSQLVLLLERLLGEGYKKKYQQVDEEFLRSDHPAILRSQARLPGFHGLRSPLDTSSVLY  
TAVQPNEGDNDYIIPLPDPKPEVADEGPLEGSPSLASSTLNEVNTSSTISCDSPLEPQDE  
PEPEPQLELQVEPEPELEQLPDSGCPAPRAEAEDSFL

SEQ ID No: 61

MGAARGSPARPRRLPLLSVLLLPLLGGTQTAIVFIKQPSSQDALQGRRALLRCEVEAPG  
PVHVYWLLDGAPVQDTERRFQAQSSLSFAAVDRLQDSGTFQCVARDDVTGEEARSAN  
ASFNIKWIEAGPVVLKHPASEAEIQPQTQVTLRCHIDGHPRPTYQWFRDGTPLSDGQSN  
HTVSSKERNLTLRPAGPEHSGLYSCCAHSAFGQACSSQNFTLSIADES FARVV LAPQD  
VVVARYEEAMFHCQFSAQPPPSLQWLFEDETPITNRSRPPHLRRATVFANGSLLLTQV  
RPRNAGIYRCIGQGQRGPPIILEATLHLAEIEDMPLFEPRVFTAGSEERVTCCLPPKGLPE  
PSVWWEHAGVRLPTHGRVYQKGHELVLANIAESDAGVYTCHAANLAGQRRQDVNITV  
ATVPSWLKKPQDSQLEEGKPGYLDCLTQATPKPTVWYRNQMLISED SRFEVFKNGTL  
RINSVEVYDGTWYRCMSSTPAGSIEAQARVQVLEKLKFTPPPQPQQCMEFDKEATVPC  
SATGREKPTIKWERADGSSLPEWVTDNAGTLHFARVTRDDAGNYTCIASNGPQQQIRA  
HVQLTVAVFITFKVEPERTTVYQGHTALLQCEAQGDPKPLIQWKKGKDRILDPTKLGPRM  
HIFQNGSLVIHDVAPEDSGRYTCIAGNSCNIKHTEAPLYVVDKPVPEESEGGPGSPPPYK  
MIQTIGLSVGA AVAYIIAVLGLMFYCKKRCKAKRLQKQPEGEPEMECLNGGPLQNGQP  
SAEIQEEVALTSLGSGPAATNKRHSTSDKMHFPRSSLQPITTLGKSEFGEVFLAKAQGL  
EEGVAETLVLVKSLQSKDEQQQLDFRRELEMFGKLNHANVVRLGLCREAEPHYMVLE  
YVDLGDLDKQFLRISKSKDEKLKSQPLSTKQKVALCTQVALGMEHLSNNRFVHKDLAARN  
CLVSAQRQVKVSALGLSKDVYNSEYYHFRQAWVPLRWMSPEAILEGDFSTKSDVWAF  
GVLMWEVFTHGEMPHGGQADDEV LADLQAGKARLPQPEGCP SKLYRLMQRCWALSP  
KDRPSFSEIASALGDSTVDSKP

SEQ ID No: 62

MGCKGDASGACAAGALPVTGVCYKMGVLVVLTVLWLFSSVKADSKAITTSLTTKWFT  
PLLLEASEFLAEDSQEKFWNFVEASQNIGSSDHDGTDYSYYHAILEAAFQFLSPLQQNL  
FKFCLSLRSYSATIQA FQQIAADEPPPEG CNSFFSVHGKKTCESDTLEALLTASERPKP  
LLFKGDHRYPSSNPESPVVIFYSEIGSEEF SNFHRQLISKSNAGKINYVFRHYIFNPRKEP

VYLSGYGVELAIKSTEYKAKDDTQVKGTEVNTTVIGENDPIDEVQGFLFGKLRDLHPDLE  
 GQLKELRKHLVESTNEMAPLKVWQLQDLSFQTAARILASPVELALVVMKDLSQNFPTKA  
 RAITKTAVSSELRTVEEENQKYFKGTLGLQPGDSALFINGLHMDLDTQDIFSLFDVLRNE  
 ARVMEGLHRLGIEGLSLHNVKLNIQPSEADYAVDIRSPAISWVNNLEVDSRYNSWPSS  
 LQELLRPTFPGVIRQIRKNLHNMVFIVDPAHETTAELMNTAEMFLSNHIPLRIGFIFVND  
 SEDVDGMQDAGVAVLRAYNYVAQEVDDYHAFQTLTHIYNKVRTGEKVKVEHVSVLEK  
 KYPYVEVNSILGIDSAYDRNRKEARGYYEQTGVGPLPVVLFNGMPFEREQLPDELETI  
 TMHKILETTTTFFQRAVYLGELPHDQDVVEYIMNQPNVVPRIINSRILTAERDYDLTASNN  
 FFVDDYARFTILDSQGKTA AVANS MNLYLTKKGMSSKEIYDDSFIRPVTFWIVGDFDSPS  
 GRQLLYDAIKHQKSSNNVRISMINNPAKEISYENTQISRAIWAALQTQTSNAAKNFITKMA  
 KEGAAEALAAGADIAEFSVGGMDFSLFKEVFESSKMDFILSHAVYCRDVLKLKKGQRAV  
 ISNGRIIGPLEDSELFNOQDDFHLLNIILKTSGQKIKSHIQQLRVEEDVASDLVMKVDALLS  
 AQPKGDPRIEYQFFEDRHSAILRKPKEGETYFDVVAVVDPVTREARLAPLLLVLALIN  
 MNLRVFMNCQSKLSDMPLKSFYRYVLEPEISFTSDNSFAKGPIAKFLDMPQSPLFTLNL  
 NTPESWMVESVRTPYDLNILEEVDSVVAEYELEYLLEGHICYDITTGQPPRGLQFT  
 LGTSANPVIVDTIVMANLGYFQLKANPGAWILRLRKGRSEDIYRIYSHDGTDSPPDADEV  
 VIVLNNFKSKIIKVKVQKKADMVNEDLLSDGTSENE SGFWDSFKWGTGQKTEEVKQD  
 KDDIINIFSVASGHLYERFLRIMMLSVLKNTKTPVKFWFLKNYLSPTFKEFIPYMANEYNF  
 QYELVQYKWPRWLHQQTEKQRIIWGYKILFLDVLFPVVDKFLFVDADQIVRTDLKELRD  
 FNLDGAPYGYTPFCDSRREMDGYRFWKSGYWASHLAGRKYHISALYVVDLKKFRKIAA  
 GDRLRGQYQGLSQDPNSLSNLDQDLPNNMIHQVPIKSLPQEWLWCETWCDDASKKRA  
 KTIDLCNNPMTKEPKLEAAVRIVPEWQDYDQEIKQLQIRFQKEKETGALYKEKTKEPSRE  
 GPQKREEL

SEQ ID No: 63

MGALARALLPLLAQWLLRAAPELAPAPFTLPLRVAAATNRVVAPTPGPGTPAERHADG  
 LALALEPALASPAGAAANFLAMVDNLQGDSSGRGYYLEMLIGTPPQKLQILVDTGSSNFAV  
 AGTPHSYIDTYFDTERSSTYRSKGFDTVKYTQGSWTGFVGEDLV TIPKGFNTSFLVNIA  
 TIFESENFFLPGIKWNGILGLAYATLAKPSSSLETFDLSLVTQANIPNVFSMQMCGAGLP  
 VAGSGTNGGSLVLGGIEPSLYKGDIWYTPIKEEWYYQIEILKLEIGGQSLNLD CREYNAD  
 KAIVDSGTTLLRLPQKVFDVAVVEAVARASLIPEFS DGFWTGSQACWTNSETPWSYFPK  
 ISIYLRDENSRSRFRITILPQLYIQPMMGAGLNYECYRFGISPSTNALVIGATVMEGFYVIF  
 DRAQKRVGFAASPCAIEIAGAAVSEISGPFSTEDVASNCVPAQSLSEPILWIVSYALMSVC  
 GAILLV LIVLLLLPFR CQRRPRDPEVVNDESSLVRHRWK

SEQ ID No: 64

MDVKERRPYCSLTKSRREKERRYTNSSADNEECRVPTQKSYSSSETLKAFDHDSSRLL  
YGNRVKDLVHREADEFTTRQGQNFTLRQLGVCEPATRRGLAFCAEMGLPHRGYSISAG  
SDADTENEAVMSPEHAMRLWGRGVKSGRSSCLSSRSNSALTLDTEHENKSDSENEQ  
PASNQGQSTLQPLPPSHKQHSQAQHPSITSLNRNSLTNRRNQSPAPPAALPAELQTP  
ESVQLQDSWVLGSNVPLESRHFLFKTGTGTTPLFSTATPGYTMASGSVYSPPTRPLPR  
NTLSRSAFKFKKSSKYCSWKCTALCAVGVSVLLAILLSYFIAMHLFGLNWQLQQTENDT  
FENGKVNSDTMPTNTVSLPSGDNGKLGFTQENNTIDSGELDIGRRAIQEIPPGIFWRS  
QLFIDQPQFLKFNISLQKDALIGVYGRKKLPPSHTQ

SEQ ID No: 65

MATQADLMELDMAMEPDRKAAVSHWQQQSYLDSGIHSGATTTAPSLSGKGNPEEEDV  
DTSQVLYEWEQGFSSFTQEQQVADIDGQYAMTRAQRVRAAMFPETLDEGMQIPSTQF  
DAAHPTNVQRLAEPSQMLKHAVVNLINYQDDAELATRAIPELTKLLNDEDQVVVNKAAV  
MVHQLSKKEASRHAIMRSPQMVSIVRTMQNTNDVETARCTAGTLHNLSHHREGLLAIF  
KSGGIPALVKMLGSPVDSVLFYAITTLHNLLHQEGAKMAVRLAGGLQKMVALLNKTNV  
KFLAITTDCLQILAYGNQESKLIILASGGPQALVNIMRTYTYEKLLWTTSRVLKVLSSVCSS  
NKPAIVEAGGMQALGLHLTDPSQRLVQNCLWTLRNLSDAATKQEGMEGLLGLTVQLLG  
SDDINVVTCAAGILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRH  
LTSRHQEAEMAQNAVRLHYGLPVVVKLLHPPSHWPLIKATVGLIRNLALCPANHAPLRE  
QGAIPRLVQLLVRAHQDTQRRRTSMGGTQQQFVEGV RMEEIVEGCTGALHILARDVHNR  
IVIRGLNTIPLFVQLLYSPIENIQRVAAGVLCELAQDKEAAEAIEAEGATAPLTELLHSRNE  
GVATYAAAVLFRMSSEDKPQDYKKRLSVELTSSLFRTEPMAWNETADLGLDIGAQGEPL  
GYRQDDPSYRSFHSGGYGQDALGMDPMMEHEMGGHHPGADYPVDGLPDLGHAQDL  
MDGLPPGDSNQLAWFDTDL

SEQ ID No: 66

MAAASYDQLLKQVEALKMENSNLRQELEDNSNHLTKLETEASNMKEVLKQLQGSIEDE  
AMASSGQIDLLERLKELNLDSSNFPGVKLRSKMSLRSYGSREGSVSSRSGECSPPVPMG  
SFPRRGFVNGSRESTGYLEELEKERSLLLADLDKEEKEKDWYYAQLQNLTKRIDSLPLT  
ENFSLQTDMTRRQLEYEARQIRVAMEEQLGTCQDMEKRAQRRIARIQQIEKDILRIRQLL  
QSQATEAERS SQNKHETGSHDAERQNEGQGVGEINMATSGNGQGSTTRMDHETASV  
LSSSSTHSAPRRLTSHLGTKIRAYCETCWEWQEAHEPGMDQDKNPMPAPVEHQICPA



VCVLMKLSFDEEHRHAMNELGGLQAIAELLQVDCEMYGLTNDHYSITLRRYAGMALTNL  
 TFGDVANKATLCSMKGCMRALVAQLKSESEDLOQVIASVLRNLSWRADVNSKKTREV  
 GSVKALMECALEVKKESTLKSVL SALWNLSAHCTENKADICAVD GALAFLVGTLTYRSQ  
 TNTLAIIESGGGILRNVSSLIATNEDHRQILRENNCLQTLLQHLKSHSLTIVSNACGTLWNL  
 SARNPKDQEALWDMGAVSMLKNLIHSHKHKMIAMGSAAALRNLMANRPAKYKDANIMSP  
 GSSLPSLHVRKQKALEAELDAQHLSETFDNIDNLSPKASHRSKQRHKQSLYGDYVFDT  
 NRHDDNRSDNFNTGNMTVLSPYLNTTVLPSSSSSRGSLDSSSRSEKDRSLERERGIGLG  
 NYHPATENPGTSSKRGLQISTTAAQIAKVMEEVSAIHTSQEDRSSGSTTELHCVTDERN  
 ALRRSSAAHTHSNTYNFTKSENSNRTCSPYAKLEYKRSSNDLSNSVSSSDGYGKRG  
 QMKPSIESYSEDDSKFCSYGQYPADLAHKIHSANHMDDNDGELDTPINYSLKYSDEQL  
 NSGRQSPSQNERWARPKHIEDEIKQSEQRQSRNQSTTYPVYTESTDDKHLKFQPHFG  
 QQECVSPYRSRGANGSETNRVGSNHGINQNVSQSLCQEDDYEDDKPTNYSERYSEEE  
 QHEEEERPTNYSIKYNEEKRHVDQPIDYSLKYATDIPSSQKQSFSFSKSSSGQSSKTEH  
 MSSSSENTSTPSSNAKRQNQLHPSSAQSRSGQPQKAATCKVSSINQETIQTYCVEDTPI  
 CFSRCSSLSSLSSAEDEIGCNQTTQEADSANTLQIAEIKEKIGTRSAEDPVSEVPAVSQH  
 PRTKSSRLQGSSLSSSESARHKAVEFSSGAKSPSKSGAQTPKSPPEHYVQETPLMFSRC  
 TSVSSLD SFESRSIASSVQSEPCSGMVSGIISPSDLPDSPGQTMPPSRSKTPPPPPQTA  
 QTKREVPKNKAPTAEKRESGPKQAAVNAAVQQRVQVLPDADTLLHFATESTPDGFSCSS  
 SLSALSLEPFIQKDVELRIMPPVQENDNGNETESEQPKESNENQEKEAEKTIDSEKDLL  
 DDSDDDDIEILEECIISAMPTKSSRKAKKPAQTASKLPPPVARPKPSQLPVYKLLPSQNR  
 LPQKHVSFTPGDDMPRVYCVGTPINFSTATSLSDLTIESPPNELAAGEGVRGGAQSG  
 EFEKRDTIPTEGRSTDEAQGGKTSSVTIPELDDNKAEEGDILAECINSAMPKGKSHKPFR  
 VKKIMDQVQQASASSAPNKNQLDGKKKKPTSPVKPIQNTTEYRTRVRKNADSKNNLN  
 AERVFSDNKDSKKQNLKNNSKDFNDKLPNNEDRVRGSAFDSPPHHTPIEGTPYCFSR  
 NDSLSSLD FDDDDVDLSREKAELRKAKENKESEAKVTSHTELTSNQQSANKTQAIKQP  
 INRGQPKPILQKQSTFPQSSKDIPDRGAATDEKLQNFAIENTPVCFSHNSSLSSLSIDIDQ  
 ENNNKENEPIKETEPDSDQGEPSKPQASGYAPKSFHVEDTPVCFSRNSSLSSLSIDSED  
 DLLQECISSAMPKKKKPSRLKGDNEKHSPRNMGGILGEDLTLDLKDQRPDSEHGLSPD  
 SENFDWKAIQEGANSIVSSLHQAAAAACLSRQASSDSDSILSLKSGISLGSPFHLTPDQE  
 EKPFTSNKGPRILKPGEKSTLETKKIESESKGIKGGKKVYKSLITGKVRNSENSEISGQMKQ  
 PLQANMPSISRGRTHIPGVRNSSSSTSPVSKKGPPLKTPASKSPSEGQTATTSPRGA  
 KPSVKSELSPVARQTSQIGGSSKAPSRSGSRDSTPSRPAQQPLSRPIQSPGRNSISPG  
 RNGISPPNKLSQLPRTSSPSTASTKSSGSGKMSYTSPGRQMSQQNLTKQTGLSKNASS  
 IPRSESASKGLNQMNNGNGANKKVELSRMSSTKSSGSESDRSERPVLVRQSTFIKEAP



SPTLRRKLEESASFESLSPSSRPASPTRSQAQTPVLSPSLPDMSLSTHSSVQAGGWRK  
LPPNLSPTIEYNDGRPAKRHDIARSHSESPSRLPINRSGTWKREHSKHSSSLPRVSTWR  
RTGSSSSILSASSESEKAKSEDEKHVNSISGTKQSKENQVSAKGTWRKIKENEFSPTN  
STSQTVSSGATNGAESKTLIYQMAPAVSKTEDVWVRIEDCPINNPRSGRSPTGNTPPVI  
DSVSEKANPNIKDSKDNQAKQNVGNGSVPMRTVGLENRLNSFIQVDAPDQKGTEIKPG  
QNNPVPVSETNESSIVERTPFSSSSSSSKHSSPSGTVAARVTPFNYNPSPRKSSADSTSA  
RPSQIPTPVNNNTKKRDSKTDSTESSGTQSPKRHSGSYLVTSV

SEQ ID No: 67

MTAVHAGNINFKWDPKSLEIRTLAVERLLEPLVTQVTTLVNTNSKGPSNKKRGRSKKAH  
VLAASVEQATENFLEKGDKIAKESQFLKEELVAVEDVRKQGDLMKAAAGEFADDPCS  
SVKRGNMVRAAPALLSAVTRLLILADMADVYKLLVQLKVVEDGILKLRNAGNEQDLGNQ  
YKALKPEVDKLNIMAAKRQQELKDVGHRDQMAAARGILQSNVPILYASQACLQHPDVA  
AYKANRDLIYKQLQQA VTGISNAAQATASDDASQHQQGGGGGELAYALNNFDKQIIVDPL  
SFSEERFRPSLEERLESIISGAALMADSSCTRDDRERIVAECNAVRQACRTC VSEYMG  
NAGRKERSDALNSAIDKMTKKTRDLRRQLRKAVMDHVSDSFLETNVPLLVLIEAAKNGN  
EKEVKEYAQVFREHANKLIEVANLAC SISNNEEGVKLVRMSASQLEAGCPQVINAATWA  
LAPKPQSKLAQENMDLFKEQWEKQVRVLTDAVDDITSIDDFLAVSENHILEDVNKCVIAL  
QEKDVDGLDRTAGAIRGRAARVIHVVTSEMDNYEPGVYTEKVLEATKLLSNTVMPRFTE  
QVEAAVEALSSDPAQPMDENEFIDASRLVYDGIRDIRKAVLMIRTPEELDDSDFETEDFD  
VRSETSVQTEDDQLIAGQSARAIMAQLPQEQKAKIREQVASFQEEKSKLDAEVSKWDD  
SGNDIIVLAKQMCMIMMEMTDFTRGKGPLKNTSDVISA AKKIAEAGSRMDKLGRTIRDH  
CPDSACKQDLLAYLQRIALYCHQLNICKVKA EVQNLGGELVVSGNCDTCGALQGLKG  
WPPPLCLATHWVDSAMSLIQAAKNLMNAV VQTVKASYVASTKYQKSQGMASLNLPAVS  
MKMKAPEKKPLVKREKQDETQTKIKRASQKKHVNPVQALSEFKAMDSI

SEQ ID No: 68

MTSATSPIILKWDPKSLEIRTLTVERLLEPLVTQVTTLVNTSNKGPSGKKKGRSKKAHVL  
AASVEQATQNFLEKGEQIAKESQDLKEELVAAVEDVRKQGETMRIASSEFADDPCSSVK  
RGTMVRAARALLSAVTRLLILADMADVMRLLSHLKIVEEAEAVKNATNEQDLANRFKEF  
GKKMVKLNYVAARRQQELKDPHCRDEMAAARGALKKNATMLYASQAFLRHPDVAAT  
RANRDYVFKQVQEA IAGISNAAQATSPTDEAKGHTGIGELAAALNEFDNKIILDPMTFSE  
ARFRPSLEERLESIISGAALMADSSCTRDDRERIVAECNAVRQALQDLLSEYMNNTGR  
KEKGDPLNIAIDKMTKKTRDLRRQLRKAVMDHISDSFLETNVPLLVLIEAAKSGNEKEVK

EYAQVFREHANKLVEVANLACISISNNEEGVKLVVRMAATQIDSLCPQVINAALTLAARPQS  
 KVAQDNMDVFKDQWEKQVRVLTEAVDDITSVDDFLSVSENHILEDVNKCVIALQEGDVD  
 TLDRTAGAIRGRAARVIHIINAEMENYEAGVYTEKVLEATKLLSETVMPRFAEQVEVAIEA  
 LSANVPQPFEENEFIDASRLVYDGVRDIRKAVLMIRTPEELEDSDSDFEQEDYDVRRGTS  
 VQTEDDQLIAGQSARAIMAQLPQEEKAKIAEQVEIFHQEKSCLKDAEVAKWDDSGNDIIVL  
 AKQMCMIMMEMTDFTRGKGPLKNTSDVINAACKIAEAGSRMDKLARAVADQCPDSACK  
 QDLLAYLQRIALYCHQLNICKSVKAEVQNLGGELIVSGTGVSQSTFTTFYEVDGCDVIDGGR  
 ASQLSTHLPTCAEGAPIGSGSSDSSMLDSATSLIQAANKLMNAVVLTVKASYVASTKYQ  
 KVYGTAAVNSPVVSWKMKAPEKKPLVKREKPEEFQTRVRRGSQKKHISPVQALSEFKA  
 MDSF

SEQ ID No: 69

MDDSEVESTASILASVKEQEAQFEKLTRALEEERRHVSAQLERVRVSPQDANPLMANG  
 TLTRRHQNGRFVGDADLERQKFSDLKLNGPQDHSLLYSTIPRMQEPGQIVETYTEED  
 PEGAMSVVSVETSDDGTTRRTETTVKKVVKTVTTRTVQPVAMGPDGLPVDASSVSNNY  
 IQTLGRDFRKNNGGPGPYVGQAGTATLPRNFHYPPDGYSRHYEDGYPGGSDNYGSL  
 SRVTRIEERYRPSMEGYRAPSQRQDVYGPQPQVRVGGSSVDLHRFHPEPYGLEDDQRS  
 MGYDDLDYGMMSDYGTARRTGTPSDPRRRLRSYEDMIGEEVPSDQYYWAPLAQHER  
 GSLASLDSLRLKGGPPPPNWRQPELPEVIAMLGFRDLDAVKSNAAYLQHLCYRNDKVKT  
 DVRKLKGIPVLVGLLDHPKKEVHLGACGALKNISFGRDQDNKIAIKNCDGVPALVRLLRK  
 ARDMDLTEVITGTLWNLSSHDSIKMEIVDHALHALTDEVIIPHSGWEREPNEDCKPRHIE  
 WESVLTNTAGCLRNVSSERSEARRKLRECDGLVDALIFIVQAEIGQKDSDSLKLVENCVC  
 LLRNLSYQVHREIPQAERYQEAAPNVANNTGPHAASCFGAKKGKGKKPIEDPANDTVD  
 FPKRTSPARGYELLFQPEVVRIYISLLKESKTPAILEASAGAIQNLCAGRWTYGRYIRSAL  
 RQEKALSAIADLLTNEHERVVKAASGALRNLAVDARNKELIGKHAIPNLVKNLPGGQQN  
 SSWNFSEDTVISILNTINEVIAENLEAAKKLRETQGIEKLVLINKSGNRSEKEVRAAALVLQ  
 TIWGYKELRKPLEKEGWKKSDFQVNLNNASRSQSSHSYDDSTLPLIDRNQKSDKKPDR  
 EEIQMSNMGSNTKSLDNNYSTPNERGDHNRTLDRSGDLGDMEPLKGTTPLMQDEGQE  
 SLEEELDVLVLDDEGGQVSYPSMQKI

SEQ ID No: 70

MCRIAGALRTLPLLLALLQASVEASGEIALCKTGFPEDVYSAVLSKDVHEGQPLLNVKF  
 SNCNGKRKVQYESSEPADFKVDEDGMVYAVRSFPLSSEHAKFLIYAQDKETQEKWQV  
 AVKLSLKPTLTEESVKESAEVEEIVFPRQFSKHSGHLQRQKRDWVIPPINLPENSRRGPF

QELVRIRSDRDKNLSLRYSVTGPGADQPPTGIFIINPISGQLSVTKPLDREQIARFHLRAH  
AVDINGNQVENPIDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDADDP  
NALNGMLRYRIVSQAPSTPSPNMFTINNETGDIITVAAGLDREKVQQYTLIIQATDMEGN  
PTYGLSNTATAVITVTDVNDNPPEFTAMTFYGEVPENRVDIIVANLTVTDKDQPHTPAW  
NAVYRISGGDPTGRFAIQTDPNNSNDGLVTVVKPIDFETNRMFVLTVA AENQVPLAKGIQ  
HPPQSTATVSVTVIDVNENPYFAPNPKIIRQEEGLHAGTMLTTFTAQDPDRYMQQNIRY  
TKLSDPANWLKIDPVNGQITTI AVL DRESPNVKNNIYNATFLASDNGIPPMSGTGTLQIYL  
LDINDNAPQVLPQEAETCETPD P NSINITALDYDIDPNAGPFAFDLPLSPVTIKRNWTITRL  
NGDFAQLNLKIKFLEAGIYEVPIIITDSGNPPKSNISILRVKVCQCDSNGDCTDVDRIVGAG  
LGTGAIIAILLCIIILLILVLMFVWWMKRRDKERQAKQLLIDPEDDV RDN ILKYDEEGGGGEED  
QDYDLSQLQQPDTVEPDAIKPVGIRRM DERPIHAEPQYPV RSAAPH PGDIGDFINEGLK  
AADNDPTAPPYDSLLVFDYEGSGSTAGSLSSLNSSSSSGGEQDYDYLNDWGPRFKKLA  
DMYGGGDD

SEQ ID No: 71

MPQLNGGGGDDL GANDELISFKDEGEQEEKSSENSSAERDLADV KSSLVNESETNQN  
SSSDSEAERRPPPRSESFRDKSRESLEEAAKRQDGGGLFKGPPYPGYPFIMIPDLTSPYL  
PNGSLSPTARTLHFQSGSTHYSAYKTIEHQIAVQYLQMKWPLLDVQAGSLQSRQALKD  
ARSPSPA HIVSNKVPVVQH PHHVHPLTPLITYSNEHFTPGNPPPHLPADVDPKTGIPRPP  
HPPDISPYYP LSPGTVGQIPHPLGWLVPQQGQP VYPITTGGFRHPYPTALT VNASMSRF  
PPHMVPPHHTLHTTGIPHPAIVTPTVKQESSQSDVGS LHSSKHQDSKKEEEKKKPHIKK  
PLNAFMLYMKEMRAKVVAECTLKESAAINQILGRRWHALSREEQAKYYELARKERQLH  
MQLYPGWSARDNYGKKKKRKRDKQPGETNEHSECFLNPCLSLPPITDLSAPKKCRARF  
GLDQQNNWCGPCRRKKKCVRYIQGEGSCLSPSSDGSLLDSPPPSPNLLGSPPRDAK  
SQTEQTQPLSLSLKPDPLAHL SMMPPPPALLAEATHKASALCPNGALDLPPAALQPAA  
PSSSIAQPSTSSLHSHSSLAGTQPQPLSLVTKSLE

SEQ ID No: 72

MEDCNVHSAASILASVKEQE ARFERLTRALEQERRHVALQLERAQQPGMVSGGMGSG  
QPLPMAWQQQLVLQE QSPGSQASLATMPEAPDVLEETVTVEEDPGTPTSHVSI VTS EDG  
TTRRTETKVTKTVKTVTTRTVRQVPVGP DGLPLLDGGPPLGPFADGALDRHFLLRGGG  
PVATLSRAYLSSGGGGFPEGPEPRDSPSYGSLSRGLGMRPPRAGPLGPGPGDGCFTLP  
GHREAFPVGPEPGPPGGRSLPERFQAEPYGLEDDTRSLAADDEGGPELEPDYGTATR  
RRPECGRGLHTRAYEDTADDGGELADERPAFPMVTAPLAQPERGSMGSLDRLVRRSP



SVDSARKEPRWRDPELPEVLAMLRHPVDPVKANAAAYLQHLCFENEGVKRRVRQLRG  
 LPLLVALLDHPRAEVRRRRACGALRNLSYGRDTDNKAAIRDCGGVPALVRLLRAARDNEV  
 RELVTGTLWNLSSYEPLKMVIIDHGLQTLTHEVIVPHSGWEREPNEDSKPRDAEWTTVF  
 KNTSGCLRVSSDGAEARRRRLRECEGLVDALLHALQSAVGRKDTDNKSVENCVCIMRN  
 LSYHVHKEVPGADRYQEAEPGPLGSAVGSQRRRRRDDASCFGGKKAKEEWFHQGKKD  
 GEMDRNFDTLDPKRTEAAKGFELLYQPEVVRLYLSLLTESRNFNTLEAAAGALQNLSA  
 GNWMWATYIRATVRKERGLPVLVELLQSETDKVVRAVAIALRNLSLDRRNKDLIGSYAM  
 AELVRNVRNAQAPPRPGACLEEDTVVAVLNTIHEIVSDSLDNARSLLQARGVPALVALV  
 ASSQSVREAKAASHVLQTVWSYKELRGTLQKDGWTKARFQSAAATAKGPKGALSPGG  
 FDDSTLPLVDKSLEGEKTGSRDVIPMDALGPDGYSTVDRRERRRPRGASSAGEASEKEP  
 LKLDPSRKAPPPGPSRPAVRLVDAVGDAKPQPVDSWV

SEQ ID No: 73

MSTETELQVAVKTSAKKDSRKKGQDRSEATLIKRFKGEGVRYKAKLIGIDEVSAARGDK  
 LCQDSMMKLKGVVAGARSKGEHKQKIFLTISFGGIKIFDEKTGALQHHAHVHEISYIAKDI  
 TDHRAFGYVCGKEGNHRFVAIKTAQAAEPVILDLRDLFQLIYELKQREELEKKAQKDKQ  
 CEQAVYQTILEEDVEDPVYQYIVFEAGHEPIRDPETEENIYQVPTSQKKEGVYDVPKSQ  
 PNSQPLEDFESRFAAATPNRNLSMDFDELLEATKVS AVTQLELFGDMSTPPDITSPPTP  
 ATPGDAFLPSSSQTLPGSADVFGSMSFGTAAVPSGYVAMGAVLP SFWGQQPLVQQQI  
 AMGAQPPVAQVIPGAQPIAWGQPGLFPATQQAWPTVAGQFPPAAFMPTQTVMPLAAA  
 MFQGPLTPLATVPGTND SARSSPQSDKPRQKMGKESFKDFQMVQPPPVP SRKPDQPS  
 LTCTSEAFSSYFNKVGVAQD TDDCDDFDISQLNLTPVTSTTPSTNSPPTPAPRQSSPSK  
 SSASHVSDPTADDIFE EGFESPSKSEEQEAPDGSQASSTSDPFGEPSPSGDNIS PQ  
 DGS

SEQ ID No: 74

MGPASPAARGLSRRPGQPPLPLLLPLLLLLLLRAQPAIGSLAGGSPGAAEAPGSAQVAGL  
 CGRLTLHRDLRTGRWEPDPQRSRRCLRDPQRVLEYCRQMYPELQIARVEQATQAIPM  
 ERWCGGSRSGSCAHPHHQVVPFRCLPGEFVSEALLVPEGCRFLHQERMDQCESSTR  
 RHQEAQEACSSQGLILHGSGMLLPCGSDRFRGVEYVCCPPPGTPDPSGTAVGDPSTR  
 SWPPGSRVEGAEDEEEEEESFPQPVDDYFVEPPQAEETVPPPSHTLAVVGKVTPT  
 PRPTDGVDIYFGMPGEISEHEGFLRAKMDLEERRMRQINEVMREWAMADNQSKNLPK  
 ADRQALNEHFQSILQTL EEQVSGERQRLVETHATRVIALINDQRRRAALEGFLAALQADPP  
 QAERVLLALRRYLRAEQKEQRHTLRHYQHVA AVDPEKAQQMR FQVHHLQVIEERVN



QSLGLLDQNPFLAQELRPQIQELLHSEHLGPSELEAPAPGGSSSEDKGGLQPPDSKDDT  
PMTLPKGSTEQDAASPEKEKMNPLEQYERKVNASVPRGFPPHSSSEIQRDELAPAGTGV  
SREAVSGLLIMGAGGGSLIVLSMLLLRRKKPYGAISHGVVEVDPMLEEQQLRELQRH  
GYENPTYRFLEERP

SEQ ID No: 75

MPRLKESRSHESLLSPSSAVEALDLSMEEEVVVKPVHSSILGQDYCFEVTTS SSGSKCFS  
CRSAAERDKWMENLRRVHPNKNDSRRVEHILKLWVIEAKDLPAKKKYLCELCLDDVL  
YARTTGKLTNDNVFWGEHFEFHNLPPLRTVTVHLYRETDK KKKKKERN SYLGLVSLPAAS  
VAGRQFVEKWYPVVTNP KGGKGP GPMIRIKARYQTITILPMEMYKEFAEHITNHYLGL  
CAALEPILSAKTKEEMASALVHILQSTGKVKDFLTDLMMSEVDRCGDNEHLIFRENTLAT  
KAIEEYLKLVGQKYLQDALGEFIKALYESDENCEVDPSKCSAADLPEHQGNLKMCCELA  
FCKIINSYCVFPRELKEVFASWRQECSSRGRPDISERLISASLFLRFLCPAIMSPSLFNLL  
QEYPDDRTARTLTIAKVTQNLANFAKFGSKEEYMSFMNQFLEHEWTNMQRFLLEISNP  
ETLSNTAGFEGYIDLGRELSSLHSLWEAVSQLEQSIVSKLGPLPRILRDVHTALSTPGS  
GQLPGTNDLASTPGSGSSSISAGLQKMVIENDLSGLIDFTRLPSPTPENKDLFFVTRSSG  
VQPSPARSSSYSEANEPDLQMANGGKSLSMVDLQDARTLDGEAGSPAGPDVLPTDGQ  
AAAQQLVAGWPARATPVNLAGLATVRRAGQTPTTPGTSEGAPGRPQLLAPLSFQNPVY  
QMAAGLPLSPRGLGDSGSEGHSSLSSHSEELAAA AKLGSFSTAAEELARRPGELAR  
RQMSLTEKGGQPTVPRQNSAGPQRRIDQPPPPPPPPPPAPRGRTPPNLLSTLQYPRP  
SSGTLASASPDWVGPPSTRLRQQSSSSSKGDSPELKPRAVHKQGPSPVSPNALDRATAAW  
LLTMNAQLLEDEGLGPDPPHRDRLRSKDELSQAEKDLAVLQDKLRISTKKLEEYETLFK  
CQEETTQKLVLEYQARLEEGEERLRRQQEDKDIQMKGIISRLMSVEEELKKDHAEMQA  
AVDSKQKIIDAQEKRIASLDAANARLMSALTQLKERYSMQARNGISPTNPTKLQITENGE  
FRNSSNC

SEQ ID No: 76

ADIISTVEFNHSGELLATGDKGGRVVIFQQEQENKIQSHSRGEYNVYSTFQSHEPEFDY  
LKSLEIEEKINKIRWLPQKNAAQFLLSTNDKTIKLWKISERDKRPEGYNLKEEDGRYRDP  
TTVTTLRVSTKKKMSQIVLVFILYSPNPEQSLNRNNYSLSPLSQPMDLMVEASPRRIFAN  
AHTYHINSISINSYETYLSADDLRINLWHLEITDRSFNIVDIK PANMEELTEVITAAEFHPN  
SCNTFVYSSSKGTIRLCDMRASALCDRHSKLFEEPEDPSNRSFFSEIISISDVKFSSHSG  
RYMMTRDYLSVKIWDNLNMENRPVETYQVHEYLRSKLCSLYENDCIFDKFELYCLFHSVV

MTGSYNNFFRMFDRNTKRDITLEASRENNKPRTVLKPRKVCASGKRKKDEISVDSLDFN  
KKILHTAWHPKENIIAVATTNNLYIF

SEQ ID No: 77

MELRVGNRYRLGRKIGSGSFGDIYLGTDIAAGEEVAIKLECVKTKHPQLHIESKIYKMMQ  
GGVGIP TIRWCGAEGDYNVMVMELLGPSLEDLFNFCSRKFSLKTVLLLADQMISRIEYIH  
SKNFIHRDVKPDNFLMGLGKKGNLVYIIDFGLAKKYRDARTHQHIPPYRENKNLTGTARYA  
SINTHLGIEQSRRDDLESLGYVLMYFNLGSLPWQGLKAATKRQKYERISEKKMSTPIEVL  
CKGYPSEFATYLNFCRSLRFDDKPDYSYLRQLFRNLFHRQGFSDYVFDWNMLKFGAS  
RAADDAERERRRDREERLRHSRNPATRGLPSTASGRLRGTQEVAPPTPLTPTSHTANTS  
PRPVSGMERERKVSMLHRGAPVNISSDLTGRQDTSRMSTSQIPGRVASSGLQSVV  
HR

SEQ ID No: 78

MAGNFDSEERSSWYWGRLSRQEAVALLQGQRHGVFLVRDSSTSPGDYVLSVSENSR  
VSHYIINSSGPRPPVPPSPAQPPPGVSPSRLRIGDQEFDSLPALEFYKIHWDTTTTLIEP  
VSRSRQSGSVILRQEEAEYVRALFDFNGNDEEDLPFKKGDILRIRDKPEEQWWNAEDS  
EGKRGMPVPYVEKYRPASASVSALIGGNQEGSHPQPLGPPEPGPYAQPSVNTPLPNL  
QNGPIYARVIQKRVPNAYDKTALALEVGELVKVTKINVSGQWEGGCNGKRGHFPFTHV  
RLLDQQNPDEDFS

SEQ ID No: 79

MGCVQCKDKEATKLTEERDGS LNQSSGYRYGTDPTPQHYP SFGVTSIPNYNNFHAAG  
GQGLTVFGGVNSSSHTGTLRTRGGTGVTLFVALYDYEARTEDDLSFHKGEKFQILNSST  
KKGKKEGPEPQEIRFAGRSDLLEG NHVDCRLVEGSADTQWMSEPQRHIHGLPDVNG  
KRWYFGKLGRKDAERQLLSFGNPRGTFLIRESETTKGAYSLSIRDWDDMKGDHVKHYK  
IRKLDNGGYITTRAQFETLQQLVQHYSERAAAGLCCRLVVPCHKGMPRLTDLSVKT KDV  
WEIPRESLQLIKRLGNGQFGEVWMGTWNGNTKVAIKTLKPGTMSPE SFLEEAQIMKKLK  
HDKLVQLYAVVSEEPYIVTEYMNKGSLLDFLKDGEGRALKLPNLVDMAAQVAAGMAYI  
ERMNYIHRDLRSANILVGNG LICKIADFG LARLIEDNEYTARQGAKFPIKWTAPEAALYGR  
FTIKSDVWSFGILLTELVT KGRVPYPGMNNREVLEQVERGYRMPCPQDCPISLHELMIH  
CWKKDPEERPTFEYLQSFL EDYFTATEPQYQPGENL

SEQ ID No: 80

MSVVGLDVGSQSCYIAVARAGGIETIANEFSDRCTPSVISFGSKNRTIGVAAKNQQITHA  
NNTVSNFKRFHGRAFNDFPIQKEKENLSYDLVPLKNGGVGIKVMYMGEEHLFSVEQITA  
MLLTKLKETAENSLKKPVTDCVISVPSFFTD AERRSVLDAAQIVGLNCLRLMNDMTAVAL  
NYGIYKQDLPSLDEKPRIVVFVDMGHSAFQVSACAFNKGKLVLTAFDPFLGGKNFDE  
KLVEHFCAEFKTKYKLDKSKIRALLRLYQECEKLKKLMSSNSTDLPLNIECFMNDKDVS  
GKMNRSQFEELCAELLQKIEVPLYSLLEQTHLKVEDVSAVEIVGGATRIPAVKERIAKFFG  
KDISTTLNADEAVARGCALQCAILSPAFAKVRFSVTDAVPFPISLIWNHDS EDTGVHEV  
FSRNHAAPFSKVLTLRRGPFLEAFYSDPQGVPEAKIGRFVQNVSAQKDGEKSR  
VKVKVRVNTHGIFTISTASMVEKVPTEENEMSSEADMECLNQRPPENPD TDKNVQQDN  
SEAGTQPQVQTDAQQT SQSPSPELTSEENKIPDADKAN EKKVDQPPEAKKPKIKVVN  
VELPIEANLVWQLGKDLLNMYIETEGKMIMQDKLEKERNDAKNAVEEYVYEF RDKLCGP  
YEKFICEQDHQNFLRLLTETEDWLYEEGEDQAKQAYVDKLEELMKIGTPVKVRFQE AEE  
RPKMFEELGQRLQHYAKIAADFRNKDEKYNHID ESEMKKVEKSVNEVMEWMNNVMNA  
QAKKSLDQDPVVRAQEIKTKIKELNNTCEPVVTQPKPKIESPKLERTPN GPNIDKKEEDL  
EDKNNFGAEP PHQNGECYPNEKNSVNMDLD

SEQ ID No: 81

MSVVGLDVGSQSCYIAVARAGGIETIANEFSDRCTPSVISFGSKNRTIGVAAKNQQITHA  
NNTVSNFKRFHGRAFNDFPIQKEKENLSYDLVPLKNGGVGIKVMYMGEEHLFSVEQITA  
MLLTKLKETAENSLKKPVTDCVISVPSFFTD AERRSVLDAAQIVGLNCLRLMNDMTAVAL  
NYGIYKQDLPSLDEKPRIVVFVDMGHSAFQVSACAFNKGKLVLTAFDPFLGGKNFDE  
KLVEHFCAEFKTKYKLDKSKIRALLRLYQECEKLKKLMSSNSTDLPLNIECFMNDKDVS  
GKMNRSQFEELCAELLQKIEVPLYSLLEQTHLKVEDVSAVEIVGGATRIPAVKERIAKFFG  
KDISTTLNADEAVARGCALQCAILSPAFAKVRFSVTDAVPFPISLIWNHDS EDTGVHEV  
FSRNHAAPFSKVLTLRRGPFLEAFYSDPQGVPEAKIGRFVQNVSAQKDGEKSR  
VKVKVRVNTHGIFTISTASMVEKVPTEENEMSSEADMECLNQRPPENPD TDKNVQQDN  
SEAGTQPQVQTDAQQT SQSPSPELTSEENKIPDADKAN EKKVDQPPEAKKPKIKVVN  
VELPIEANLVWQLGKDLLNMYIETEGKMIMQDKLEKERNDAKNAVEEYVYEF RDKLCGP  
YEKFICEQDHQNFLRLLTETEDWLYEEGEDQAKQAYVDKLEELMKIGTPVKVRFQE AEE  
RPKMFEELGQRLQHYAKIAADFRNKDEKYNHID ESEMKKVEKSVNEVMEWMNNVMNA  
QAKKSLDQDPVVRAQEIKTKIKELNNTCEPVVTQPKPKIESPKLERTPN GPNIDKKEEDL  
EDKNNFGAEP PHQNGECYPNEKNSVNMDLD

SEQ ID No: 82

MAAADGDDSLYPIAVLIDELRNEDVQLRLNSIKKLSTIALALGVERTRSELLPFLTDTIYDE  
 DEVLALAEQLGTFTTLVGGPEYVHCLLPPLSLATVEETVVRDKAVESLRAISHEHSPS  
 DLEAHFVPLVKRLAGGDWFTSRTSACGLFSVCYPRVSSAVKAELRQYFRNLCSDDTPM  
 VRRAAASKLGEFAKVLELDNVKSEIIPMFSNLASDEQDSVRLLAVEACVNIAQLLPQEDL  
 EALVMPTLRQAAEDKSWRVRYMVADKFTTELQKAVGPEITKTDLVPAFQNLMDCEAEV  
 RAAASHKVKEFCENLSADCENVIMSQILPCIKELVSDANQHVKSALASVIMGLSPILGK  
 DNTIEHLLPLFLAQLKDECPEVRLNIISNLDVNEVIGIRQLSQSLLPAIVELAEDAKWRVR  
 LAIIEYMPLLAGQLGVEFFDEKLNSLCMAWLVDHVYAIREAATSNLKKLVEKFGKEWAHA  
 TIIPKVLAMSGDPNYLHRMTTLFCINVLESEVCGQDITTKHMLPTVLRMAGDPVANVRFNV  
 AKSLQKIGPILDNSTLQSEVKPILEKLTQDQDQDVVKYFAQEALTVLSLA

SEQ ID No: 83

MSVPSSLSQSAINANSHGGPALSPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGEGG  
 GPEPGPANAKWLKEGQNQLRRAATAHRDQNRNVTLTAAEEASQEPPEMAPLGPKGLIHL  
 YSELELSAHNAANRGLRGPGLIISTQEQGPDEGEEKAAGEAEEEEEDDDDEEEEEEDLS  
 SPPGLPEPLESVEAPPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
 SYGSPEDTDSFWNPNAFETDSDLPAGWMRVQDTSGTYYYWHIPTGTTQWEPPGRASP  
 SQGSSPQEESQLTWTGFAHGEGFEDGEFWKDEPSDEAPMELGLKEPEEGTLTFPAQS  
 LSPEPLPQEEEEKLPPRNTNPGIKCFAVRSLGWVEMTEEELAPGRSSVAVNNCIRQLSYH  
 KNNLHDPMSGGWGEGKDLLLQLEDETLKLVEPQSQALLHAQPIISIRVWGVGRDSGRE  
 RDFAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICKSKIMAERRNARCLVNGLSLDHS  
 KLVDVPPFQVEFPAPKNELVQKFQVYYLGNVPVAKPVGVVDVINGALESVLSSSSREQWT  
 PSHVSVAPATLTILHQQTEAVLGEQVRFLSFLAVGRDVHTFAFIMAAGPASFCCHMFW  
 CEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWTVRRGVQS  
 LWGSLKPKRLGAHTP

SEQ ID No: 84

MSVPSSLSQSAINANSHGGPALSPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGEGG  
 GPEPGPANAKWLKEGQNQLRRAATAHRDQNRNVTLTAAEEASQEPPEMAPLGPKGLIHL  
 YSELELSAHNAANRGLRGPGLIISTQEQGPDEGEEKAAGEAEEEEEDDDDEEEEEEDLS  
 SPPGLPEPLESVEAPPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
 SYGSPEDTDSFWNPNAFETDSDLPAGWMRVQDTSGTYYYWHIPTGTTQWEPPGRASP  
 SQGSSPQEESQLTWTGFAHGEGFEDGEFWKDEPSDEAPMELGLKEPEEGTLTFPAQS  
 LSPEPLPQEEEEKLPPRNTNPGIKCFAVRSLGWVEMTEEELAPGRSSVAVNNCIRQLSYH



KNNLHDPMSGGWGEGKDLLLQLEDETLKLVEPQSQALLHAQPIISIRVWGVGRDSGRE  
RDFAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICSKIMAERRNARCLVNGLSLDHS  
KLVDVPPFQVEFPAPKNELVQKFQVYYLGNVPVAKPVGVVDVINGALESVLSSSSREQWT  
PSHVSVPATLTILHQQTEAVLGECRVRFLSFLAVGRDVHTFAFIMAAGPASFCCHMFW  
CEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWTVRRGVQS  
LWGSLKPKRLGAHTP

SEQ ID No: 85

MDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSI  
HHGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No: 86

MDFQHRPGGKTGSGGVASSSESNRDRRERLRQLALETIDINKDPYFMKNHLGSYECKL  
CLTLHNNEGSYLAHTQGKKHQTNLARRAAKEAKEAPAQPAPEKVKVEVKKFVKIGRPG  
YKVTKQRDSEMGQQSLLFQIDYPEIAEGIMPRHRFMSAYEQRIEPPDRRWQYLLMAAE  
PYETIAFKVPSREIDKAEGKFWTHWNRETQFFLQFHFMEKPPAPPSLPAGPPGVKR  
PPPPLMNGLP RPPLPESLPPPPPGGLPLPMPPTGPAPSGPPGPPQLPPPAPGVHPP  
APVVHPPASGVHPPAPGVHPPAPGVHPPAPGVHPPTSGVHPPAPGVHPPAPGVHPPA  
PGVHPPAPGVHPPAPGVHPPPSAGVHPQAPGVHPAAPAVHPQAPGVHPPAPGMHPQ  
APGVHPQPPGVHPSAPGVHPQPPGVHPSNPGVHPPTPMPPMLRPPLPSEGPGNIPPP  
PPTN

SEQ ID No: 87

MLGKDYMLAILVNCDDDLWGDHSLEVEAGLPPGWRKIHDAAGTYYYWHVPSGSTQWQ  
RPTWELGDAEDPGTGTEGIWGLRPPKGRSFSSLESSLDRSNSLSWYGGESYIQSMEP  
GAKCFAVRSLGWVEVPEEDLAPGKSSIAVNNCIQQLAQTRSRSQPPDGAWGEGQNML  
MILKKDAMSLVNPLDHSLIHCQPLVHIRVWGVGSSKGRFYPSPIAPARDFAFVASDKD  
SCMLKCHVFCCDVPKAIASALHGLCAQILSERVEVSGDASCCSPDPISPEDLPRQVEL  
LDAVSQAAQKYEALYMGTLPTVKAMGMDVLNEAIGTLTARGDRNAWVPTMLSVSDSL  
MTAHPIQAEASTEEEPLWQCPVRLVTFIGVGRDPHTFGLIADLGRQSFQCAAFWCQPH  
AGGLSEAVQAACMVQYQKCLVASAARGKAWGAQARARLRKRTSSMDSPGGPLPLPL  
LKGGVGGAGATPRKRGVFSFLDAFRLKPSLLHMP

SEQ ID No: 88

MEVDGTPRRGGCKMPLPVQVFNLQGAVEPMQIDVDPQEDPQNAPDVNYVVENPSLDL  
 EQYAASYSGLMRIERLQFIADHCPTLRVEALKMALSFVQRTFNVDMEYEEIHRKLSEATR  
 ELQNAPDAIPESGVEPPALDTAWVEATRKKALLKLEKLDLKNYKGNSIKESIRRGHDD  
 LGDHYLDCGDLNALKCYSRARDYCTSAKHVINMCLNVIKVSVYLQNWSHVLSYVSKA  
 ESTPEIAEQRGERDSQTQAILTKLKCAAGLAELAARKYKQAAKCLLLASFDHCDPPELLS  
 PSNVAIYGGLCALATFDRQELQRNVISSSSFKLFLELEPQVRDIIFKFYESKYASCLKMLD  
 EMKDNLLLDMYLAPHVRTLYTQIRNRALIQYFSPYVSADMHRMAAAFNTTVAAEDEL  
 QLILEGLISARVDSHSHKILYARDVDQRSTTFEKSLLMGKEFQRRRAKAMMLRAAVLRNQIH  
 VKSPPREGSQGELTPANSQSRMSTNM

SEQ ID No: 89

MSDMEDDFMCDDEEDYDLEYSEDSNSEPNDLENQYYNSKALKEDDPKAALSSFQKV  
 LELEGEKGEWGFKALKQMIKINFKLTFPEMMNRYKQLLTYIRSAVTRNYSEKSINSILD  
 YISTSKQMDLLQEFYETTLKDAKNDRLWFKTNTKLGLYLEREEYGKLQKILRQLHQ  
 SCQTDDGEDDLKKGTTQLLEIYALEIQMYTAQKNNKKLKALYEQSLHIKSAIPHPLIMGVIR  
 ECGGKMHLREGEFEKAHTDFFEAFKNYDESGSPRRTTCLKYLVLANMLMKSGINPFDS  
 QEAKPYKNDPEILAMTNLVSAYQNNDITEFEKILKTNHSNIMDDPFIREHIEELLRNIRTQV  
 LIKLIKPYTRIHIPFISKELNIDVADVESLLVQCILDNTIHGRIDQVNQLLELDHQKRGARY  
 TALDKWTNQLNSLNQAVVSKLA

SEQ ID No: 90

MAAAVRQDLAQLMNSSGSHKDLAGKYRQILEKAIQLSGAEQLEALKAFVEAMVNENVS  
 LVISRQLLTDFCTHLPNLPDSTAKEIYHFTLEKIQPRVISFEEQVASIRQHLSIYEKEEDW  
 RNAAQVLVGIPLETGQKQYNVDYKLETYLLKIARLYLEDDDPVQAEAYINRASLLQNESTN  
 EQLQIHYKVCYARVLDYRRKFIEAAQRYNELSYKTIVHESERLEALKHALHCTILASAGQ  
 QRSRMLATLFKDERCQQLAAYGILEKMYLDRIIRGNQLQEFAAMLMPHQKATTADGSSI  
 LDRAVIEHNLLSASKLYNNITFEELGALLEIPAAKAEKIASQMITEGRMNGFIDQIDGIVHF  
 ETREALPTWDKQIQSLCFQVNNLLEKISQTAPEWTAQAMEAQMAQ

SEQ ID No: 91

MAASGSGMAQKTWELANNMQEAQSIDEIYKYDKKQQQEILANLGTKDHHYFKYCKIS  
 ALALLKMVMHARSGGNLEVMGLMLGKVDGETMIIMDSFALPVEGTETRVNAQAAAYEY  
 MAAYIENAKQVGRENAIGWYHSHPGYGCWLSGIDVSTQMLNQQFQEPFVAVVIDPTR  
 TISAGKVNLGAFRTYPKGYKPPDEGPSEYQTIPLNKIEDFGVHCKQYYALEVSYFKSSLD

RKLLELLWNKYWVNTLSSSSLLTNADYTTGQVFDLSEKLEQSEAQLGRGSFMLGLETH  
DRKSEDKLAKATRDSCKTIEAIHGLMSQVIKDKLFNQINIS

SEQ ID No: 92

MAAAAAAATNGTGGSSGMEVDAAVPSVMACGVTGSVSVALHPLVILNISDHWIRM  
RSQEGRPVQVIGALIGKQEGRNIEVMNSFELLSHTVEEKIIDKEYYYTKEEQFKQVFKEL  
EFLGWYTTGGPPDPSDIHVHKQVCEIIESPLFLKLNPMTKHTDLPVSVFESVIDIINGEAT  
MLFAELTYTLATEEAERIGVDHVARMTATGSGENSTVAEHLIAQHSAIKMLHSRVKLILEY  
VKASEAGEVPFNHEILREAYALCHCLPVLSTDKFKTDFYDQCNDVGLMAYLGTITKTCN  
TMNQFVNKFNVLYDRQGIGRRMRGLFF

SEQ ID No: 93

MSAEVKVTGQNQEQLLLAKSAKGAALATLIHQVLEAPGVYVFGELLDMPNVRELAESD  
FASTFRLLTVFAYGTYADYLAEARNLPPLTEAQKNKLRHLSVVTLAAKVKCIPYAVLLEAL  
ALRNVRLQLEDLVIEAVYADVLRGSLDQRNQRLEVDYSIGRDIQRQDLSAIARTLQEWCV  
GCEVVLSGIEEQVSRANQHKEQQLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQH  
LTELREPAPGTNQRQPSKKASKGKGLRGSAKIWSKSN

SEQ ID No: 94

MPVAVMAESAFSFKKLLDQCENQELEAPGGIATPPVYGQLLALYLLHNDMNNARYLWK  
RIPPAIKSANSELGGIWSVGQRIWQRDFPGIYTTINAHQWSETVQPIMEALRDATRRRAF  
ALVSQAYTSIIADDFAAFVGLPVEEAVKGILEQGWWQADSTTRMVLPRKPVAGALDVSN  
KFIPLSEPAPVPPIPNEQQLARLTDYVAFLEN

SEQ ID No: 95

MLIKVKTLTGKEIEIDIEPTDKVERIKERVEEKEGIPPQQQRLIYSGKQMNDEKTAADYKIL  
GGSVLHLVLALRGGGGLRQ

SEQ ID No: 96

MAAAMDVDTPSGTNSGAGKKRFEVKKWNAVALWAWDIVVDNCAICRNHIMDLCECQA  
NQASATSEECTVAWGVCNHAFHFHCISRWLKTRQVCPLDNREWEFQKYGH

SEQ ID No: 97

MDADM DYERPNVETIKCVVVG DNAV GKTR LICARACNTT LTQYQL LATHVPTVW AIDQY  
 RVCQEVLERSRDVVDEVSVSLRLWDTFGDHHKDRRFAYGRSDVVVLCFSIANPNSLNH  
 VKSMWYPEIKHFCPRTPVILVGCQLDLRYADLEAVNRARRPLARPIKRGDILPPEKGREV  
 AKELGLPYYETSVFDQFGIKDVFDNAIRAALISRRHLQFWKSHLKKVQKPLLQAPFLPPK  
 APPVVIKIECPSMGTNEAACLLDNPLCADVLFILQDQEHIFAHRIYLATSSSKFYDLFLM  
 ECEESPNGSEGACEKEKQSRDFQGRILSVDPEEEEREEGPPRIPQADQWKSSNKSLVEA  
 LGLEAEGAVPETQTLTGWSKGFIMHREM QVNPISKRMGPMTVVRMDASVQPGPFRT  
 LLQFLYTGQLDEKEKDLVGLAQIAEVLEMFDLRMMVENIMNKEAFMNQEITKAFHVRKA  
 NRIKECLSKGTFSDVTFKLDDGAISAHKPLLICSEWMAAMFGGSFVESANSEVYLPNIN  
 KISMQAVLDYLYTKQLSPNLDLDPLELIALANRFCLPHLVALAEQHAVQELTKAATSGVGI  
 DGEVLSYLELAQFHNAHQLAAWCLHHICTNYNSVCSKFRKEIKSKSADNQEYFERHRW  
 PPVWYLKEEDHYQRVKREREKEDIALNKHRSRRKWCFWNSSPAVA

SEQ ID No: 98

ACSAGRDVFLTLEATPSHVVSRLMDSDMDYERPNVETIKCVVVG DNAV GKTR LICARA  
 CNATLTQYQL LATHVPTVW AIDQYRVCQEVLERSRDVVDDVSVSLRLWDTFGDHHKDR  
 RFAYGRSDVVVLCFSIANPNSLHHVKT MWYPEIKHFCPRAPVILVGCQLDLRYADLEAV  
 NRARRPLARPIKPNEILPPEKGREVAKELGIPYYETSVVAQFGIKDVFDNAIRAALISRRH  
 LQFWKSHLRNVQRPLLQAPFLPPKPPPPIIVVPDPPSSSEECPAHLLEDPLCADVILVLQ  
 ERVRIFAHKIYLTSSSKFYDLFLMDLSEGELGGPSEPGGTHPEDHQGHSDQH HHHHHH  
 HHHGRDFLLRAASFDCESVDEAGGSGPAGLRASTSDGILRGNGTGYLPGRGRVLSS  
 WSRAFVSIQEEMAEDPLTYKSRLMVVVKMDSSIQPGPFRAVLKYLYTGELDENERDLM  
 HIAHIAELLEVFDLRMMVANILNNEAFMNQEITKAFHVRRRTNRVKECLAKGTFSDVTFILD  
 DGTISAHKPLLISSCDWMAAMFGGPFVESSTREVVFPYTSKSCMRVLEYLYTGMFTSS  
 PDLDDMKLIILANRLCLPHLVALTEQYTVTGLMEATQMMVDIDGDVLVFLELAQFHCAYQ  
 LADWCLHHICTNYNNVCRKFPRDMKAMSPENQEYFEKHRWPPVWYLKEEDHYQRAR  
 KEREKEDYLHLKRQPKRRWLFWNSSPSSSAASSSSPSSSSAVV

SEQ ID No: 99

KSIVKIRNRMAAETQTLNFGPEWLRLALSSGGSITSPPLSPALPKYKLADYRYGREMLAL  
 FLKDNKIPSDLLDKEFLPILQEEPLPPLALVPFTEEEQRNFSMSVNSAAVLRLTGRGGGG  
 TVVGAPRGRSSSRGRGRGRGECGFYQRSFDEVEGVFGRGGG REMHRSQSWEERGD  
 RRFKPKGRKDVGKKNGYYCMYSPVLLL GQPLCQGRPNFEEGGPTSVGRKHEFIRSES  
 ENWRIFREEQNGEDEDGGWRLAGSRRDGERWRPHSPDGPRSAGWREHMERRRRFE



FDFRDRDDERGYRRVRSGSGSIDDDRDSLPEWCLEDAEEEMGTFDSSGAFLSLKKVQ  
 KEPIPEEQEMDFRPVDEGEECSDSEGSHNEEAKEPDKTNKKEGEKTDRVGVASEETP  
 QTSSSSARPGTPSDHQSQEASQFERKDEPKTEQTEKAEETRMENSLPAKVPSRGDE  
 MVADVQQPLSQIPSDTASPLLLPPPVPNPSPTLRPVETPVVGAPGMGVSSTEPDDEEG  
 LKHLEQQAEMVAYLQDSALDDERLASKLQEHRAKGVSIPLMHEAMQKWYYKDPQGEI  
 QGPFNNQEMAWEWFQAGYFTMSLLVKRACDESQPLGDIMKMWGRVPFSPGPAPPPH  
 MGELDQERLTRQQELTALYQMQLQYQQFLIQQQYAQVLAQQQKAALSSQQQQQLAL  
 LLQQFQTLKMRISDQNIIPSVTRSVSVPDTGSIWELQPTASQPTVWEGGSVWDLPLDTT  
 TPGPALEQLQQLEKAKAAKLEQERREAEMRAKREEEERKRQEELRRQQEEILRRQQEE  
 ERKRREEEELARRKQEEALRRQREQEIALRRQREEEERQQQEEALRRLEERRREEEE  
 RRKQEELLRKQEEEAAKWAREEEEEAQRRLEENRLRMEEEAARLRHEEEERKRKELEV  
 QRQKELMRQRQQQQEALRRLLQQQQQQQQLAQMKLPSSSTWGQQSNTTACQSQATL  
 SLAEIQKLEEEERERQLREEQRRQQRELMKALQQQQQQQQQKLSGWGNVSKPSGTTK  
 SLLEIQQEEARQMOKQQQQQQQHQQPNRARNNTHSNLHTSIGNSVWGSINTGPPNQ  
 WASDLVSSIWSNADTKNSNMGFWD DAVKEVGPRNSTNKNKNNASLSKSVGVSNRQN  
 KKVEEEEKLLKLFQGVNKAQDGFTQWCEQMLHALNTANNLDVPTFVSFLKEVESPYEV  
 HDYIRAYLGDTSEAKEFAKQFLERRAKQKANQQRQQQQQLPQQQQQQQPPQQPPQQPQ  
 QQDSVWGMNHSTLHSVFQTNQSNQSNFEAVQSGKKKKKKQKMVRADPSLLGFSVN  
 ASSERLNMGEIETLDDY

SEQ ID No: 100

MRLTRCQAALAAAITLNLVLFYVSWLQHQPNSRARGPRRASAAGPRVTVLVREFEA  
 FDNAVPELVDSFLQQDPAQPVVVAADTLPPYPLALPRIPNVRLALLQPALDRPAAASRP  
 ETYVATEFVALVPDGARAEAPGLLERMVEALRAGSARLVAAPVATANPARCLALNVSLR  
 EWTARYGAAPAAPRCDALDGDVLLRARDLFNLSAPLARPVGTSLFLQTALRGWAVQ  
 LLDLTFAAARQPPLATAHARWKAEREGRARRAALLRALGIRLVSWEGGRLEWFGCNKE  
 TTRCFGTVVGDTPAYLYEERWTPPCCLRALRETARYVVGVLAAAGVRYWLEGGSLGA  
 ARHGDIIPWDYDVDLGIYLEDVGNCEQLRGAEAGSVVDERGFVWEKAVEGDFFRVQYS  
 ESNHLHVDLWPFYPRNGVMTKDTWLDHRQDVEFPEHFLQPLVPLPFAGFVAQAPNNY  
 RRFLELKFGPGVIENPQYPNPALLSLTGSG

SEQ ID No: 101

HLPKQQRGGVCLGVKSKWQPKLRTGREKIINMHFQAFWLCLGLLFISINAEFMDDDVET  
 EDFEENSEEIDVNESELSSEIKYKTPQPIGEVYFAETFDSGRLAGWVLSKAKKDDMDEEI

SIYDGRWEIEELKENQVPGDRGLVLKSRAXHHAISAVLAKPFIFADKPLIVQYEVNFQDGI  
DCGGAYIKLLADTDDLILENFYDKTSYIIMFGPDKCGEDYKLHFIFRHKHPKTGVFEEKHA  
KPPDVDLKKFFTDNRKTHLYTLVMNPDDTFEVLVDQTVVNKGSLLLEDVVPPIKPPKEIEDP  
NDKKPEEWDERAKIPDPSAVKPEDWDESEPAQIEDSSVVKPAGWLDDEPKFIPDPNAE  
KPDDWNEDTDGEWEAPQILNPACRIGCGEWKPPMIDNPKYKGVWRPPLVDNPNYQGI  
WSPRKIPNPDYFEDDHPFLLTSFSALGLELWSMTSDIYFDNFIICSEKEVADHWAADGW  
RWKIMIANANKPGVLKQLMAAAEGHPWLWLIYLVTAGVPIALITSFCWPRKVKKKHKDT  
EYKKTDCIPQTKGVLEQEEKEEKAALPKPMDLEEEKKQNDGEMLEKEEESEPEEKSEE  
EIEIEGQEESENQSNKSGSEDEMKEADESTGSGDGPIKSVRKRRVRKD

SEQ ID No: 102

MRCCHICKLPGRVMGIRVLRLSLVVILVLLLAVAGALTALLPSVKEDKMLMLRREIKSQGK  
STMDSFTLIMQTYNRTDLLLKLLNHQYQAVPNLHKVIVVWNNIGEKAPDELWNSLGPHPIP  
VIFKQQTANRMRNRLQVFPELETNAVLMVDDDTLISTPDLVFAFSVWQQFPDQIVGFVP  
RKHVSTSSGIYSYGSFEMQAPGSGNGDQYSMVLIGASFFNSKYLELFQRQPAAVHALID  
DTQNCDDIAMNFIIAKHIGKTSGIFVKPVNMDNLEKETNSGYSGMWHRAEHALQRSYCI  
NKLVNIYDSMPLRYSNIMISQFGFPYANYKRKI

SEQ ID No: 103

MRCCHICKLPGRVMGIRVLRLSLVVILVLLLAVAGALTALLPSVKEDKMLMLRREIKSQGK  
STMDSFTLIMQTYNRTDLLLKLLNHQYQAVPNLHKVIVVWNNIGEKAPDELWNSLGPHPIP  
VIFKQQTANRMRNRLQVFPELETNAVLMVDDDTLISTPDLVFAFSVWQQFPDQIVGFVP  
RKHVSTSSGIYSYGSFEMQAPGSGNGDQYSMVLIGASFFNSKYLELFQRQPAAVHALID  
DTQNCDDIAMNFIIAKHIGKTSGIFVKPVNMDNLEKETNSGYSGMWHRAEHALQRSYCI  
NKLVNIYDSMPLRYSNIMISQFGFPYANYKRKI

SEQ ID No: 104

MAERRRHKKRIQEVGEPSKEEKAVAKYLRFCPTKSTNMMGHRVDYFIASKAVDCLLD  
SKWAKAKKGEEALFTTRESVVDYCNRLKKQFFHRALKVMKMKYDKDIKKEKDKGKAE  
SGKEEDKKSKKENIKDEKTKKEKEKKKDGEKEESKKEETPGTPKKKETKKKFKLEPHDD  
QVFLDGNEVYVWIYDPVHFKTFVMGLILVIAVIAATLFPLWPAEMRVGVYYLSVGAGCFV  
ASILLAVARCILFLIWLITGGRHHFWFLPNLTADVGFIDSFRPLYTHEYKGPKADLKKDE  
KSETKKQKSDSEEKSDSEKKEDEEGKVGPGNHGTEGSGGERHSDDSDRREDDRS  
QHSSGNGNDFEMITKEELEQQTDGDCEEDEEEENDGETPKSSHEKS

SEQ ID No: 105

MGCKGDASGACAAGALPVTGVCYKMGVLVVLTVLWLFSSVKADSKAITTSLTTKWFST  
PLLEASEFLAEDSQEKFWNFVEASQNIGSSDHDGTDYSYYHAILEAAFQFLSPLQQNL  
FKFCLSLRSYSATIQAFQQIAADEPPPEG CNSFFSVHGKKTCESDTLEALLLTASERPKP  
LLFKGDHRYPSSNPESPVVIFYSEIGSEEF SNFHRQLISKSNAGKINYVFRHYIFNPRKEP  
VYLSGYGVELAIKSTEYKAKDDTQVKGTEVNTTVIGENDPIDEVQGFLFGKLRDLHPDLE  
GQLKELRKHLVESTNEMAPLKVWQLQDLSFQTAARILASPVELALVVMKDLSQNFPTKA  
RAITKTAVSSEL RTEVEENQKYFKGTLGLQPGDSALFINGLHMDLDTQDIFSLFDVLRNE  
ARVMEGLHRLGIEGLSLHNVLKLNIPSEADYAVDIRSPAISWVNNLEVDSRYNSWPSS  
LQELLRPTFPGVIRQIRKNLHNMFIVDPAHETTAELMNTAEMFLSNHIPLRIGFIFVND  
SEDVDGMQDAGVAVL RAYNYVAQEVDDYHAFQTLTHIYNKVRTGEKVKVEHVSVLEK  
KYPYVEVNSILGIDSAYDRNRKEARGYYEQTG VGPLPVVLFNGMPFEREQ LDPDELETI  
TMHKILETTTFFQRAVYLGELPHDQDVVEYIMNQPNVVPRINSRILTAERDYDLTASN  
FFVDDYARFTILDSQGKTA AVANS MNYLTKKGMSSKEIYDDSFIRPVTFWIVGDFDSPS  
GRQLLYDAIKHQKSSNNVRISM INNPAKEISYENTQISR AIWAALQTQTSNAAKNFITKMA  
KEGAAEALAAGADIAEF SVGGMDFSLFKEVFESSKMDFILSHAVYCRDVLKLKKGQRAV  
ISNGRIIGPLEDSELFNQDDFHLL ENIILKTSGQKIKSHIQQLRVEEDVASDLVMKVDALLS  
AQP KGDPRIEYQFFEDRHS AIKLRPKEGETYFDVVAVVDPVTRE AQRLAPLLL VLAQLIN  
MNL RVFMNCQSKLS DMPLKS FYRYVLEPEISFTSDNSFAKGPIAKFLDMPQSPLFTLNL  
NTPESWMVESVRTPYDL DNIYLEEVDSVVA AEYELEYLLLEGHCYDITTGQPPRGLQFT  
LGTSANPVIVDTIVMANLGYFQLKANPGAWILRLRKGRSEDIYRIYSHDGTDSPPDADEV  
VIVLNNFKSKIIKVKVQKKADMVNEDLLSDGTSENE SGFWD SFKWGFTGQKTEEVKQD  
KDDIINIFSVASGHLYERFLRIMMLSVLKNTKTPVKFWFLKNYLSPTFKEFIPYMANEYNF  
QYELVQYKWPRWLHQQTEKQRIIWGYKILFLDVLFPLVVDKFLFVDADQIVRTDLKELRD  
FNLDGAPYGYTPFCDSRREMDGYRFWKSGYWASHLAGRKYHISALYVVDLKKFRKIAA  
GDRLRGQYQGLSQDPNSLSNLDQDLPNNMIHQVPIKSLPQEWLWCETWCDDASKKRA  
KTIDLCNNPMTKEPKLEAAVRIVPEWQDYDQEIKQLQIRFQKEKETGALYKEKTKEPSRE  
GPQKREEL

SEQ ID No: 106

MSGGGPSGGGPGGSGRARTSSFAEPGGGGGGGGGGGGPGGSASGPGGTGGGKASVG  
AMGGGVGASSSGGGPGGSGGGGGSGGPGAGTSFPPPGVKLGRDSGKVTTVVATLGQ  
GPERSQEVAYTDIKVIGNGSFGVVYQARLAETRELVAIKKVLDKRFKNRELQIMRKLDH



CNIVRLRYFFYSSGEKKDELYLNLVLEYVPETVYRVARHFTKAKLTIPILYVKVYMYQLFR  
 SLAYIHSQGVCHRDIKPQNLLVDPDTAVLKLCDFGSAKQLVRGEPNVSYICSRYYRAPE  
 LIFGATDYTSSIDVWSAGCVLAELLGQPIFPGDSGVDQLVEIHKVLGTPTREQUIREMNP  
 YTEFKFPQIKAHPWTKVFKSRTPPEAIALCSSLLEYTPSSRLSPLEACAHSFFDELRCLG  
 TQLPNNRPLPPLFNFSAGELSIQPSLNAILIPPHLRSPAGTTTTLTPSSQALTETPTSSDWQ  
 STDATPTLTNSS

SEQ ID No: 107

MNIQEQGFPLDLGASFTEDAPRPPVPGEEGELVSTDPRPASYSFCSGKGVGKGETST  
 ATPRRSDLDLGYEPEGSASPTPPYLKWAESLHSLDDQDGLSLFRTFLKQEGCADLLDF  
 WFACTGFRKLEPCDSNEEKRLKLARAIYRKYILDNNGIVSRQTKPATKSFIKGCIMKQLID  
 PAMFDQAQTEIQATMEENTYPSFLKSDIYLEYTRTGSESPKVCSDQSSGSGTGKGISGY  
 LPTLNEDEEWKCDQDMDDEDGRDAAPPGRLPQKLLLETAAPRVSSSRRYSEGREFRY  
 GSWREPVNPYYVNAGYALAPATSANDSEQQSLSSDADTLSLTDSSVDGIPPYRIRKQH  
 RREMQUESVQVNGRVPLPHIPRTYRVPKEVRVEPQKFAEELIHRLEAVQRTREAEKLEE  
 RLKRVRMEEEGEDGDPSSGPPGPCHKLPAPAWHHFPPRCVDMGCAGLRDAHEENP  
 ESILDEHVQRVLRTPGRQSPGPGHRSPDSGHVAKMPVALGGAASGHGKHVPKSGAKL  
 DAAGLHHHRHVHHHVHHSTARPKEQVEAEATRRAQSSFAWGLEPHSHGARSRGYSE  
 SVGAAPNASDGLAHSGKVGVAACKRNAKKAESGKSASTEVPGASEDAEKNQKIMQWIE  
 GEKEISRHRRTGHGSSGTRKPQPHENSRLSLEHPWAGPQLRTSVQPSHLFIQDPTMP  
 PHPAPNPLTQLEEARRRLEEEEEKRASRAPSKQRYVQEVMMRRGRACVRPACAPVLHV  
 PAVSDMELSETETRSQRKVGGGSAQPCDSIVVAYYFCGEPIPYRTLVRGRAVTLGQFK  
 ELLTKKGSYRYYFKKVSDEFDCGVVFEEVREDEAVLPVFEEKIIGKVEKVD

SEQ ID No: 108

MPCRREEEEEAGEEEAEGEEEEEDSFLLLQQSVALGSSGEVDRLVAQIGETLQLDAAXD  
 SPASPCGPPGAPLRAPGPLAAVPADKARSPAVPLLLPPALAETVGPAPPGLVRCALG  
 DRGRVRGRAAPYCVAEATGPSALSPLPPQADLDGPPGAGKQGIPQPLSGPCRRGWL  
 RGAAASRRLQQRREGSQPETRTGDDDPHRLQLQLVLSGNLIKEAVRRLHSRRLQLRAKL  
 PQRPLLGPLSAPVHEPPSPRSPRAACSDPGASGRAQLRTGDGVLVPGS

SEQ ID No: 109

MPCRREEEEEAGEEEAEGEEEEEDSFLLLQQSVTLGSSGEVDRLVAQIGETLQLDAAQD  
 SPASPCAPPVPLRAPGPLAAVPADKARPPAVPLLLPPASAETVGPAPSGALRCALG



DRGRVRGRAAPYCVAEVAAGPSALPGPCRRGWLRDAVTSRRLQQRRWTQAGARAG  
DDDPHRLQLQLVLSGNLIKEAVRRLQRAVAAVAATGPASAPGPGGGGRSGPDRIALQPS  
GSL

SEQ ID No: 110

MNVQEQGFPLDLGASFTEDAPRPPVPGEEGELVSTDSRPVNHSFCSGKGTSIKSETST  
ATPRRSDLDLGYEPEGSASPTPPYLRWAESLHSLDDQDGLSLFRTFLKQEGCADLLDF  
WFACSGFRKLEPCDSNEEKRLKLARAIYRKYILDSNGIVSRQTKPATKSFIKDCVMKQQI  
DPAMFDQAQTEIQSTMEENTYPSFLKSDIYLEYTRTGSESPKVCSDQSSGSGTGKGMS  
GYLPTLNEDEEWKCDQDADEDDGRDSVPPSRLTQKLLLETAAPRAPSSRRYNEGREL  
RYGSWREPVNPYYVNSGYALAPATSANDSEQQSLSSDADTSLTDSSVDGIPPYRIRK  
QHRREMQESVQVNGRVPLPHIPRTYRMPKEIRVEPQKFAEELIHRLEAVQRTREAEKL  
EERLKRVRMEEEGEDGEMPSGPMASHKLPSVPAWHHFPPRYVDMGCSGLRDAHEEN  
PESILDEHVQRVMRTPGCQSPGPGHRSPDSGHVAKTAVLGGTASGHGKHAPKLGLKL  
DSAGLHHHRHVHHHVHHNSARPKEQMEAEAARRVQSSFSWGPETHGHAKPRSYSES  
TGTNPSAGDLAFGGKASAPSKRNTKKAESGKNASAEVPSTTEDAEKNQKIMQWIEGE  
KEISRHRKAGHGSSGMRKQQAHESSRPLSIERPGAVHPWVSAQLRNSVQPSHLFIQDP  
TMPPNPAPNPLTQLEEARRRLEEEEEKRANKLPSKQRTKSQRKAGGGSAPPCDSIVVAY  
YFCGEPIPYRTLVRGRAVTLGQFKELLTKKGSYRYYFKKVSDEFDCGVVFEEVREDEAI  
LPVFEEKIIGKVEKVD

SEQ ID No: 111

MATFRNNHMKTKASVRKSFSQSVKSLLSQKELCSVTAEDCLQQDEHANLTEVT  
FLGFNEETDAAHIQDLAAVSLELPDILNSLHFCSLNENEIICMKNINKPLDISSDPLNQSH  
SGMLCVMRVSPSPRLRIDFIFSLLSKYATGIRYTLDTFLHQKHQLETTDEDDDDTNQSV  
SSIEDDFVTAFEHLEEEETSKPYNDGMNITVLRSCDAASQTVTGHHLETHDLKILISSG  
QQKSLAKPSTSSVNLGHKELPSVKTSVTTSISEPWTQRSFYRSSNASDKDSDLQKTFF  
SSSPAYSSSESECSSPSPVIFLDEEGYQKSLKAKLELPKIPVMKDDIEDSDSEVSEFFDSF  
DQFDELEQTLETCLFNKDPVIGKSSQRKGKHGKSCMNPQKFKFDRPALPANVRKPTP  
RKPESPYGNLCDAPDSPRPVKASREDSGLFSPIRSSAFSPLGGCTPAECFCQTDIGGD  
RIHENHDSVYYTYEDYAKSISCEVLGSLRTHHTNTLSNINSIKHGENKTVTFKHGNLDQ  
KNKSKNKSLMIKDSIQKFAADLVEKSFGSAFKDLQKGVSSCTNALYHLAIKLTSSVLQMA  
FDELRRQRAFSKERAISGLANFLVSEALSNAKDLQYVKKQIFTNTVARFAADLAEELV  
FEGIMEVCQFSYPQTPASPQCGSFDKVVKLYAKDLSESVIQEAFIELSQVDVTFTTK

AAVSVSTDNIKYVSAESVVPSTQAVTFSPSFHNQAIMVTKPVQEYKKEYTVQQALFCTS  
 GIVTSIPVPLAGSALLPYHISSTACQAKAHLSSDDSNSNGDSAQVHIATKNREEKAACLR  
 NICLPSEHNPGNQNDFKPTNDDIEMQSSSKLPNDPAIISNFSAAVVHTIVNETLESMTSL  
 EVTKMVDERTDYLTKSLKEKTPPFSHCDQAVLQCSEASSNKDMFADRLSKSIIKHSIDKS  
 KSVIPNIDKNAVYKESLPVSGEESQLTPEKSPKFPDSQNQLTHCSLSAAKDCVPECKVS  
 MVHGSSLETLPSCPAVTGQKSDLKESAKDQPLKKHNLNSTSLEALSFGQENPFPHSHT  
 FSSTALTCVDGLHVEDKQKVRDRNVIPDTPPSTPLVPSRASSEWDIKKLTKKLKGELAK  
 EFAPATPPSTPHNSSVGSLSENEQNTIEKEEFMLKLMRSLSEEVESSESSELPEVDVKS  
 EHSKGVQFAEALATHILSLATEMAASHLDNKIIQEPKVKNPCLNVQSQRSVSPTFLNPS  
 DENLKTLCNFAGDLAAEVITEAEKIAKVRNCMLFKQKKNSCYADGDEDYKVEEKLDIEAV  
 VHPREVDPFILSLPPSSCMSGLMYKYPSCSVTDEYAGHLIQILKQEGGNSELIMDQYA  
 NRLAYRSVKSGLQEAAKTTKVQCNSRMFPVPSSQVKTNKELLMFSNKEHHQEADKKR  
 QSKRNEGYFCKNQT CERTLDPYRNEVSQLYSFSTSLVHSITKDAKEELTASLVGLPKSL  
 TDSCLFEKSGYEEDNECHVTPELPKSLQPSSQNHRFYHSTGSLNGYGCGDNVVQAVE  
 QYAKKVDDTLELT LGSTVFRVSETTKSADRVTYAEKLSPLTGQACRYCDLKELHNCTG  
 NSSQHFFRQGLASSKPPASNPKESSRYQKSRIHLSVPQIHVNLDKKAVLAEKIVAEAE  
 KAERELSSTSLAADSGIGQEGASFAESLATETMTAAVTNVGHAVSSSKEIEDFQSTESV  
 SSQQMNLSIGDDSTGWSNLSFEDEHQDESSSFHHLSESNNGNSSSWSSLGLEGDLYE  
 DNLSFPTSDSDGPDDKDEEHEDEVEGLGQDGKTLITNIDMEPCTVDPQLRIILQWLIAS  
 EAEVAELYFHDSANKEFMLLSKQLQEKGWKVGDLLQAVLQYYEVMKASSEERCKSLF  
 DWLLENA

SEQ ID No: 112

METDCNPMELSSMSGFEEGSELNGFEGTDMKDMRLEAEAVVNDVLFVNNMFVSKSL  
 RCADDVAYINVETKERNRYCLELTEAGLKVVGYAFDQVDDHLQTPYHETVYSLDLTSP  
 AYREAFGNALLQRLEALKRDGQS

SEQ ID No: 113

TSSRAVCSAAAAAAAAAALSVWPAGPVGVCSTRTDEQRVAVLRQLEMSEPKAIDPKLSTT  
 DRVVKAVPFPSSHRLTAKEVFDNDGKPRVDILKAHLMKEGRLEESVALRIITEGASILRQ  
 EKNLLDIDAPVTVCGLIHGQFFDLMKLFEVGGSPANTRYLFLGDYVDRGYFSIECVLYL  
 WALKILYPKTLFLLRGNHECRHLTEYFTFKQECKIKYSERVYDACMDAFDCLPLAALMN  
 QQFLCVHGGLSPEINTLDDIRKLDRFKEPPAYGPMCDILWSDPLEDFGNEKTQEHFTHN  
 TVRGCSYFYSYPVCEFLQHNNLLSILRAHEAQDAGYRMYRKSQTTGFPSLITIFSAPNY

LDVYNNKAAVLKYENNVNMNIRQFNCSHPYWLPNFMDFVFTWSLPFVGEKVTEMLVNVL  
NICSDDDELGSEEDGFDGATAAARKEVIRNKIRAIGKMARVFSVLREESESVLTLKGLTPT  
GMLPSGVLSGGKQTLQSATVEAIEADEAIKGFSPQHKITSFEEAKGLDRINERMPPRRD  
AMPSDANLNSINKALTSETNGTDSNGSNSNNIQ

SEQ ID No: 114

MAAPEPARAAPPPPPPPPPPGADRVVKAVPFPPTHRLTSEEVFDLDGIPRVDVLKNHL  
VKEGRVDEEIALRIINEGAAILRREKTMIEVEAPITVCGDIHGQFFDLMKLFEVGGSPANT  
RYLFLGDYVDRGYFSIEHVLGTEDISINPHNNINECVLYLWVLKILYPSTLFLLRGNHECR  
HLTEYFTFKQECKIKYSERVYEACMEAFDSLPLAALLNQQFLCVHGGLSPEIHTLDDIRR  
LDRFKEPPAFGPMCDLLWSDPSEDFGNEKSQEHFSHNTVRGCSYFYNYPAVCEFLQN  
NNLLSIIRAHEAQDAGYRMYRKSQTTGFPSLITIFSAPNYLDVYNNKAAVLKYENNVMMNI  
RQFNCSHPYWLPNFMDFVFTWSLPFVGEKVTEMLVNVLSICSDDDELMTEGEDQFDGS  
AAARKEIIRNKIRAIGKMARVFSVLREESESVLTLKGLTPTGMLPSGVLAGGRQTLQSGN  
DVMQLAVPQMDWGTPHSFANNSHNACREFLLFFSSCLSS

SEQ ID No: 115

MVDYSVWDHIEVSDDDEDETHPNIDTASLFRWRHQARVERMEQFQKEKEELDRGCRCR  
KRKVAECQRKLKELEVAEGGKAELERLQAEAAQLRKEERSWEQKLEEMRKKEKSMPW  
NVDTLSDGFSKSMVNTKPEKTEEDSEEVREQKHKTFFVEKYEKQIKHFGMLRRWDDS  
QKYLSDNVHLVCEETANYLVIWCIDLEVEEKCALMEQVAHQTIMQFILELAKSLKVDPR  
ACFRQFFTKIKTADRQYMEGFNDELEAFKERVGRRAKLRIEKAMKEYEEEEERKKRLGP  
GGLDPVEVYESLPEELQKCFDVKDQMLQDAISKMDPTDAKYHMQRCIDSGLWVPNS  
KASEAKEGEEAGPGDPLLEAVPKTGDEKDVS

SEQ ID No: 116

MHFRNFNYSFSSLIACVANSDFSESETRAKFESLFRTYDKDITFQYFKSFKRVRINFSNP  
FSAADARLQLHKTEFLGKEMKLYFAQTLHIGSSHLAPPNPDQFLISPPASPPVGWKQV  
EDATPVINYDLLYAISKLGPGKEYELHAATDTTPSVVVHVCESDQEKEEEEEEMERMRRP  
KPKIIQTRRPEYTPIHLS

SEQ ID No: 117

MGNAAAAGKKGSEQESVKEFLAKAKEDFLKKWESPAQNTAHLQFERIKTLGTGSFGRV  
MLVKHKETGNHYAMKILDKQKVVKLKQIEHTLNEKRILQAVNFPFLVKLEFSFKDNSNLY

MVMEYVPGGEMFSHLRRIGRFSEPHARFYAAQIVLTFEYLHSLDLIYRDLKPENLLIDQQ  
GYIQVTDGFGFAKRVKGRTWTLCGTPEYLAPEIILSKGYNKAVDWWALGVLIYEMAAGYP  
PFFADQPIQIYEKIVSGKVRFP SHFSSDLKDLLRNLLQVDLTKRFGNLKNGVNDIKNHKW  
FATTDWIAIYQRKVEAPFIPKFKGPGDTSNFDDYEEEEIRVSINEKCGKEFSEF

SEQ ID No: 118

GNAATAKKGSEVESVKEFLAKAKEDFLKKWENPTQNNAGLEDFERKKT LGTGSFGRV  
MLVKHKATEQYYAMKILDKQKVVKLKQIEHTLNEKRILQAVNFPFLVRLEYAFKDNSNLY  
MVMEYVPGGEMFSHLRRIGRFSEPHARFYAAQIVLTFEYLHSLDLIYRDLKPENLLIDHQ  
GYIQVTDGFGFAKRVKGRTWTLCGTPEYLAPEIILSKGYNKAVDWWALGVLIYEMAAGYP  
PFFADQPIQIYEKIVSGKVRFP SHFSSDLKDLLRNLLQVDLTKRFGNLKNGVSDIKTHKW  
FATTDWIAIYQRKVEAPFIPKFRGSGDTSNFDDYEEEDIRVSITEKCAKEFGEF

SEQ ID No: 119

MESGSTAASEEARSLRECELYVQKHNIQALLKDSIVQLCTARPERPMAFLREYFERLEK  
EEAKQIQNLQKAGTRTDSREDEISPPPPNPVVKGRRRRRG AISAEVYTEEDAASYVRKVI  
PKDYKTMAALAKAIEKNVLF SHLDDNERSDIFDAMFSVSFIAGETVIQQGDEGDNFYVID  
QGETDVYVNNEWATSVGEGGSFGELALIYGTPRAATVKAKTNVKLW GIDRDSYRRILM  
GSTLRKRKMYEEFLSKVSILES LDKWERLTVADALEPVQFEDGQKIVVQGE PGDEFFIIL  
EGSAAVLQRRSENEEFVEVGRLGPSDYFGEIALLMNRPRAATV VARGPLKCVKLD RPR  
FERVLGPCSDILKRNIQQYNSFVSLSV

SEQ ID No: 120

MLTCNKAGSRMVVDAANSNGPFQP VVLLHIRDVPPADQEKLF IQKLRQCCVLFDFVSD  
PLSDLKWKEVKRAALSEMVEYITHNRNVITEPIYPEVVHMF AVNMFR TLPPSSNPTGAE  
FDPEEDEPTLEAAWPHLQLVYEFFLR FLESPDFQPNI AKKYIDQKFVLQLLELFDSEDPR  
ERDFLKTTLHRIYGKFLGLRAYIRKQINNIFYRFIYETEH HNGIAELLEILGSIINGFALPLKE  
EHKIFLLKVLLPLHKVKSLSVYHPQLAYCVVQFLEKDSTL TEPVVMALLKYWP KTHSPKE  
VMFLNELEEILDVIEPSEFVKIMEPLFRQLAKCVSSPHFQVAERALYYWNNEYIMSLISDN  
AAKILPIMFPSLYRNSKTHWNKTIHGLIYNALKLF MEMNQKLFDDCTQQFKA EKLKEKLK  
MKEREEAWVKIENLAKANPQVLKKRIT

SEQ ID No: 121



MEDYLQGCRAALQESRPLHVVLGNEACDLDSTVSALALAFYLAKTTEAEEVFVPVLNIK  
 RSELPLRGDIVFFLQKVHIPSILIFRDEIDLHALYQAGQLTLILVDHHILSKSDTALEEAVA  
 EVLDHRPIEPKHCPPCHVSVELVGSCATLVTERILQGAPEILDRQTAALLHGTIILDCVNM  
 DLKIGKATPKDSKYVEKLEALFPDLPKRNDIFDSLQKAKFDVSGLTTEQMLRKDQKTIYR  
 QGVKVAISAIYMDLEAFLQRSNLLADLHAFCAHSYDVLVAMTIFFNTHNEPVRQLAIFC  
 PHVALQTTICEVLERSHSPPLKLTPASSTHPNLHAYLQGNTQVSRKKLLPLLQEALSAYF  
 DSMKIPSGQPETADVSREQVDKELDRASNSLISGLSQDEEDPPLPPTPMNSLVDECPLD  
 QGLPKLSAEAVFEKCSQISLSQSTTASLSKK

SEQ ID No: 122

MAERESGGLGGGAASPPAASPFLGLHIASPPNFRLTHDISLEEFEDDLSEITDECGISL  
 QCKDTLSLRPPRAGLLSAGGGGAGSRLQAEMLQMDLIDATGDTPGAEDDEEDDDEER  
 AARRPGAGPPKAESGQEPASRGQGQSQGQSQGGPGSGD TYRPKRPTTLNLFQVPRS  
 QDTLNNNSLGKKHSWQDRVSRSSSPLKTGEQTPPHEHICLSDELPPQSGPAPTDRGT  
 STDSPCRRSTATQMAPPGGPPAAPPGGRGHSRDRIH YQADVRL EATEEIY LTPVQRP  
 PDAAEPTSAFLPPTESRMSVSSDPDPAAYPSTAGRPHPSISEEEEGFDCLSSPERAEPP  
 GGGWRGSLGEPPPPPRASLSSDTSALSYDSVKYTLVVDEHAQLELVSLRPCFGDYSDE  
 SDSATVYDNCASVSSPYESAIGEEYEEAPRPQPPACLSDESTPDEPDVHFSKKFLNVF  
 MSGRSRSSSAESFGLFSCIINGEEQEQT HRAIFRFVPRHEDELELEVDDPLLVELQAED  
 YWYEAYNMRTGARGVFPAYYAIEVTKEPEHMAALAKNSDWVDQFRVKFLGSVQVPYH  
 KGNDVLCAAMQKIATTRRLTVHFNPPSSCVLEISVRGVKIGVKADDSQEAKGNKCSHFF  
 QLKNISFCGYHPKNNKYFGFITKHPADHRFACHVFVSEDSTKALAESVGRAFQQFYKQF  
 VEYTCPTEDIYLE

SEQ ID No: 123

MSTMVYIKEDKLEKLTQDEIISKTKQVIQGLEALKNEHNSILQSLLET LKCLKKDDESNLV  
 EEKSNMIRKSLEMLELGLSEAQVMMALSNHLNAVESEKQKLRAQVRRLCQENQWLRD  
 ELANTQQKLQKSEQSVAQLEEEKKHLEFMNQLKKYDDDISPSEDKDTDSTKEPLDDLFP  
 NDEDDPGQGIQQQHSSAAAAAQGGGYEIPARLRTLHNLVIQYASQGRYEVAVPLCKQA  
 LEDLEKTSBGHDHPDVATMLNILALVYRDQNKYKDAANLLNDALAIREKTLGKDHPAVAAT  
 LNNLAVLYGKRGKYKEAEPLCKRALEIREKVLGKDHPDVAKQLNNLALLCQNQGKYEEV  
 EYYYQRALEIYQTKLGPDDPNVAKTKNNLASCYLKQGKFKQAETLYKEILTRAHEREFG  
 SVDDENKPIWMHAEEREECKGKQKDGT SFGEYGGWYKACKVDSPTVTTTLKNLGALY

RRQ GKFEAAETLEEAAMRSRKQGLDNVHKQRVAEVLNDPENMEKRRSRESLNVDVVK  
YESGPDGGEEVSMMSVEWNGGVSGRASFCGKRQQQQWPGRRRHR

SEQ ID No: 124

MADPAECSIKVMCRFRPLNEAEILRGDKFIPKFKGDETVVIGQGKPYVFDRVLPPNTTQE  
QVYNACAKQIVKDVLEGYNGTIFAYGQTSSGKTHTMEGKLHDPQLMGIIPRIAHDFDHIY  
SMDENLEFHIKVSYFEIYLDKIRDLLDVSKTNLAVHEDKNRVPYVKGCTERFVSSPEEVM  
DVIDEGKANRHVAVTNMNEHSSRSHSIFLINIKQENVETEEKLSGKLYLVDLAGSEKVS  
TGAEGAVLDEAKNINKSLSALGNVISALAEAGTKTHVPYRDSKMTRILQDSLGGNCRTTIV  
CCSPSVFNEAETKSTLMFGQRAKTIKNTVSVNLELTAEWKKKYEKEKEKNKTLKNVIQ  
HLEMELNRWRNGEAVPEDEQISAKDQKNLEPCDNTPIIDNIAPVVAGISTEEKEYDEEI  
SSLYRQLDDKDDEINQQSQLAEKLLKQQMLDQDELLASTRRDYEKIQEELTRLQIENEAA  
KDEVKEVLQALEELAVNYDQKSQEVEDKTRANEQLTDELAQKTTTLTTTQRELSQLQEL  
SNHQKKRATEILNLLLKDLGEIGGIIGTNDVKTLADVNGVIEEEFTMARLYISKMKSEVKSL  
VNRSKQLESAQMDSNRKMNASERELAACQLLISQHEAKIKSLTDYMQNMEQKRRQLEE  
SQDSLSEELAKLRAQEKMHVSFQDKEKEHLTRLQDAEEMKKALEQQMESHREAHQK  
QLSRLRDEIEEKQKIIDEIRDNLQKLQLEQEKLSDDYNKLKIEDQEREMKLEKLLLLNDKR  
EQARED LKGLEETVSRELQTLHNLRLKLFVQDLTTRVKKSVELDNDGGSAAQKQKISF  
LENNLEQLTKVHKQLVRDNADLRCELPKLEKRLRATAERVKALESALKEAKENAMRDRK  
RYQQEVDRIKEAVRAKNMARRAHSAQIAKPIRPGHYPASSPTAVHAIRGGGGSSSNST  
HYQK

SEQ ID No: 125

MADLAECNIKVMCRFRPLNESEVNRGDKYIAKFQGEDTVVIASKPYAFDRVFQSSTSQE  
QVYNDCAKKIVKDVLEGYNGTIFAYGQTSSGKTHTMEGKLHDPEGMGIIPRIVQDIFNYI  
YSMDENLEFHIKVSYFEIYLDKIRDLLDVSKTNLSVHEDKNRVPYVKGCTERFVCSPDEV  
MDTIDEGKSNRHVAVTNMNEHSSRSHSIFLINVKQENTQTEQKLSGKLYLVDLAGSEKV  
SKTGAEGAVLDEAKNINKSLSALGNVISALAEAGSTYVPYRDSKMTRILQDSLGGNCRTTI  
VICCSPSSYNESETKSTLLFGQRAKTIKNTVCVNVELTAEQWKKKYEKEKEKNKILRNTI  
QWLENELNRWRNGETVPIDEQFDKEKANLEAFTVDKDITLTNDKPATAIGVIGNFTDAE  
RRKCEEEIAKLYKQLDDKDEEINQQSQLVEKLKTQMLDQEELLASTRRDQDNMQAELN  
RLQAENDASKEEVKEVLQALEELAVNYDQKSQEVEDKTKEYELLSDELNQKSATLASID  
AELQKLKEMTNHQKKRAAEMMASLLKDLAEIGIAVGNNNDVKQPEGTGMIDEEFTVARLY  
ISKMKSEVKTMVKRCKQLESTQTESNKKMEENEKELAACQLRISQHEAKIKSLTEYLQN

VEQKKRQLEESVDALSEELVQLRAQEKVHEMEKEHLNKVQTANEVKQAVEQQIQSHRE  
 THQKQISSLRDEVEAKAKLITDLQDQNKMMLEQERLRVEHEKLNKATDQEKSRKLHELT  
 VMQDRREQARQDLKGLEETVAKELQTLHNLRKLFVQDLATRVKKS AEIDSDDTGGSAA  
 QKQKISFLENNLEQLTKVHKQLVRDNADLRCELPKLEKRLRATAERVKALESALKEAKE  
 NASRDRKRYQQEVDRIKEAVRSKNMARRGHS AQIAKPIRPGQH PAASPTHPSAIRGGG  
 AFVQNSQPVAVRGGGGGKQV

SEQ ID No: 126

MATQADLMELDMAMEPDRKAAVSHWQQQSYLD SGIHSGATTTAPSLSGKGNPEEEDV  
 DTSQVLYEWEQGFSQSFTQEQVADIDGQYAMTRAQRVRAAMFPETLDEGMQIPSTQF  
 DAAHPTNVQRLAEPSQMLKHAVVNLINYQDDAELATRAIPELTKLLNDEDQVVVNKAAV  
 MVHQLSKKEASRHAIMRSPQMVS AIVRTMQNTNDVETARCTAGTLHNLSHHREGLLAIF  
 KSGGIPALVKMLGSPVDSVLFYAITTLHNLLLHQEGAKMAVRLAGGLQKMVALLNKTNV  
 KFLAITTDCLQILAYGNQESKLIILASGGPQALVNIMRTYTYEKLLWTTSRVLKVLSSVCSS  
 NKPAIVEAGGMQALGLHLTDPSQRLVQNCLWTLRNLSDAATKQEGMEGLLGTLVQLLG  
 SDDINVVTCAAGILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRH  
 LTSRHQEAEMAQNAVRLHYGLPVVVKLLHPPSHWPLIKATVGLIRNLALCPANHAPLRE  
 QGAIPRLVQLLVRAHQDTQRRRTSMGGTQQQFVEGVRMEEIVEGCTGALHILARDVHNR  
 IVIRGLNTIPLFVQLLYSPIENIQRVAAGVLCELAQDKEAAEAIEAEGATAPLTELLHSRNE  
 GVATYAAAVLFRMSEDKPQDYKKRLSVELTSSLFRTPEMAWNETADLGLDIGAQGEPL  
 GYRQDDPSYRSFHS GGGYGQDALGMDPMMEHEMGGHHPGADYPVDGLPDLGHAQDL  
 MDGLPPGDSNQLAWFDTDL

SEQ ID No: 127

MSSSEEVSWISWFCGLRGNEFFCEVDEDYIQDKFNLTGLNEQVPHYRQALDMILDLEP  
 DEELEDNPNQSDLIEQA AEMLYGLIHARYILTNRGIAQM LEKYQQGDFGYCPRVYCENQ  
 PMLPIGLSDIPGEAMVKLYCPKCMDVYTPKSSRHHHTDGAYFGTGFP HMLFMVHPEYR  
 PKRPANQFVPRLYGFKIHPMAYQLQLQAASNFKSPVK TIR

SEQ ID No: 128

MSWVQATLLARGLCRAWGGTCGAALTGTSISQVPRRLPRGLHCSAAAHSSEQSLVPS  
 PPEPRQRPTKALVPFEDLFGQAPGGERDKASFLQTVQKFAEHSVRKRGHIDFIYLALRK  
 MREYGVERDLAVYNQLLNIFPKEVFRPRNIIQRIFVHYPRQQECGI AVLEQMENHGVMP  
 NKETEFLLIQIFGRKSY PMLKLVRLKLWFPRFMNVNPFVPRDLPQDPVELAMFGLRHM



EPDLSARVTIYQVPLPKDSTGAADPPQPHIVGIQSPDQQAALARHNPARPVFVEGPFSL  
WLRNKCYYHILRADLLPPEEREVEETPEEWNLYYPMQLDLEYVRSGWDNYEFDINEV  
EEGPVFAMCMAGAHDQATMAKWIQGLQETNPTLAQIPVVFRLAGSTRELQTSSAGLEE  
PPLPEDHQEEDDNLQRQQQGQS

SEQ ID No: 129

MFFSMGFIVAVKGKIASPLEAPVFVAAPHSTFFDGIACVVAGLPSMVSRNENAQVPLIGR  
LLRAVQPVLVSRVDPDSRKNTINEIHKRTTSGGEWPQILVFPEGTCTNRSCITFKPGAFI  
PGVPVQPVLLRYPNKLDTVTWTWQGYTFIQLCMLTFCQLFTKVEVEFMPVQVPNDEEK  
NDPVLFANKVRNLMAEALGIPVTDHTYEDCRLMISAGQLTLPMEAGLVEFTKISRKLKLD  
WDGVRKHLDEYASIASSSKGGRIGIEEFAKYLLKLPVSDVLRQLFALFDRNHDGSIDFREY  
VIGLAVLCNPSNTEEIIQVAFKLFDVDEDDGYITEEEFSTILQASLGVPDLDVSGLFKEIAQG  
DSISYEEFKSFALKHPEYAKIFTTYLDLQTCHVFSLPKEVQTTTPSTASNKVSPEKHEEST  
SDKKDD

SEQ ID No: 130

MAATALLEAGLARVLFYPTLLYTLFRGKVPGRAHRDWDYHRIDPTVLLGALPLRSLTRQLV  
QDENVRGVITMNEEYETRFLCNSSQEWKRLGVEQLRLSTVDMTGIPTLDNLQKGVQFA  
LKYQSLGQCVYVHCKAGRSRSATMVAAYLIQVHKWSPEEAVRAIAKIRSYIHIRPGQLDV  
LKEFHKQITARATKDGTFFVSKT

SEQ ID No: 131

MTKFGFLRLSYEKQDTLLKLLILSMAAVLSFSTRLFAVLRFESEVIHEFDPYFNYRTTRFLA  
EEGFYKFHNWFDDRAWYPLGRIIGGTIYPGLMITSAAIYHVLHFFHITIDIRNVCVFLAPLF  
SSFTTIVTYHLTKELKDAGAGLLAAAMIAVVPGYISRSVAGSYDNEGIAIFCMLLTYYMWI  
KAVKTGSICWAAKCALAYFYMVSSWGGYVFLINLIPLHVLVLMLTGRFSHRIYVAYCTVY  
CLGTILSMQISFVGFPVLSSEHMAAFGVFGLCQIHAFVDYLRSKLNPQQFEVLFRSVIS  
LVGFVLLTVGALLMLTGKISPWTGRFYSLDPSYAKNNIPIIASVSEHQPTTWSSYYFDLQ  
LLVFMFPVGLYYCFSNLSARIFIMYGVTSMYFSAVMVRMLVLAPVMCILSGIGVSQVL  
STYMKNLDISRPDKKSKKQQDSTYPIKNEVASGMILVMAFFLITYTFHSTWVTSEAYSSP  
SIVLSARGGDGSRIIFDDFREAYYWLRHNTPEDAKVMSWWDYGYQITAMANRTILVDNN  
TWNNTTHISRVGQAMASTEELKAYEIMRELDVSYVLVIFGGLTGYSSDDINKFLWMVRIGG  
STDTGKHIKENDYYTPTGEFRVDREGSPVLLNCLMYKMCYYRFGQVYTEAKRPPGFDR  
VRNAEIGNKDFELDVLEEAYTTEHWLVRIYKVKDLDNRGLSRT



SEQ ID No: 132

MNLERSNEEKLNLCKRYLGGFAFLPFLWLVNIFWFFREAFSLVPAYTEQSQIKGYVWR  
SAVGFLFWVIVLTSWITIFQIYRPRWGALGDYLSFTIPLGTP

SEQ ID No: 133

EAPGSSVKPVLCLHSAARAGKWSLGSGAEQQRLSPGPPVPSLTCLPSARMATITCTRF  
TEEYQLFEELGKGAFSVVRRVCVKVLAGQEYAAKIINTKKLSARDHQKLEREARICRLLKH  
PNIVRLHDSISEEGHHYLIFDLVTGGELFEDIVAREYYSEADASHCIIQQILEAVLHCHQMG  
VVHRDLKPENLLLASKLKGA AVKLADFGLAIEVEGEQQAWFGFAGTPGYLSPEVLRKDP  
YGKPVDLWACGVILYILLVGYPPFWDEDQHRLYQQIKAGAYDFPSPEWDTVTPEAKDLI  
NKMLTINPSKRITAAEALKHPWISHRSTVASCMHRQETVDCLKKFNARRKLKGAILTTML  
ATRNFSGGKSGGNKKSDGVKESSESTNTTIEDEDTKVRKQEIIKVTEQLIEAISNGDFES  
YTKMCDPGMTAFEPEALGNLVEGLDFHRFYFENLWSRNSKPVHTTILNPHIHLMGDES  
ACIAYIRITQYLDAGGIPRTAQSEETRVWHRRDGKWQIVHFHRSGAPSVLPH

SEQ ID No: 134

MAAQCVTKVALNVSCANLLDKDIGSKSDPLCVLFLNTSGQQWYEVERTERIKNCLNPQF  
SKTFIIDYYFEVVQKLKFGVYDIDNKTIELSDDDFLGECECTLGQIVSSKKLTRPLVMKTG  
RPAGKGSITISAEIKNRVVLFEMEARKLDNKDLFGKSDPYLEFHKQTS DGNWLMVHR  
TEVVKNLNPVWRPFKISLNSLCYGDMDKTIKVECYDYDNDGSHDLIGTFQTTMTKLKE  
ASRSSPVEFECINEKKRQKKKSYKNSGVISVKQCEITVECTFLDYIMGGCQLNFTVGVDF  
TGSNGDPRSPDSLHYISPNGVNEYLTALWSVGLVIQDYDADKMFPAPFGFGAQIPPQWQ  
VSHEFPMNFNPSNPYCNGIQGIVEAYRSCLPQIKLYGPTNFSPIINHVARFAAAATQQQT  
ASQYFVLLIITDGVITDLDETRQAIVNASRLPMSIIIVGVGGADFSAMEFLDGDGGSLSRPL  
GEVAIRDIVQFVPFRQFQNAPEALAQCVLAEIPQQVVG YFNTYKLLPPKNPATKQQKQ

SEQ ID No: 135

RRRRPSSSRRLRGRGAAQMACPALGLEALQPLQPEPPPEPAFSEAQKWIEQVTGRSF  
GDKDFRTGLENGILLCELLNAIKPGLVKKINRLPTPIAGLDNIILFLRGCKELGLKESQLFD  
PSDLQDTSNRVTVKSLDYSRKLKNVLVTIYWLGAANSCTSYSGTTNLKEFEGLLAQM  
RKDTDDIESPKRSIRDSGYIDCWDSERSDSLSPPRHGRDDSFDSLDSFGSRSRQTPSP  
DVVLRGSSDGRGSDSESDLPHRKLDPVKKDDMSARRTSHGEPKSAVPFNQYLPNKS  
QTAYVPAPLRKKKAEREEYRKSWSTATSPLGGERPFRYGPRTPVSDDAESTSMFDMR

CEEEAAVQPHSRARQEQLQLINNQLREEDDKWQDDLARWKSRRRSVSQDLIKKEEER  
 KKMEKLLAGEDGTSERRKSIKTYREIVQEKERRERELHEAYKNARSQEEAEGILQQYIE  
 RFTISEAVLERLEMPKILERSHSTEPNLSSFLNDPNPMKYLRQQSLPPPKFTATVETTIAR  
 ASVLDTSMSAGSGSPSKTVTPKAVPMLTPKPYSQPKNSQDVLKTFKVDGKVSVNGETV  
 HREEEKERECPTVAPAHSLTKSQMFEGVARVHGSPLELKQDNGSIEINIKKPNSVPQEL  
 AATTEKTEPNSQEDKNDGGKSRKGNIELASSEPHFTTTTVTRCSPTVAFVEFPSSPQLK  
 NDVSEEKQKKPENEMSGKVELVLSQKVVKPKSPEPEATLTFPFLDKMPEANQLHLPN  
 LNSQVDSPSSEKSPVTTPQFKFWAWDPEEERRRQEKWQQEQERLLQERYQKEQDKL  
 KEEWEKAQKEVEEEEERRYYEEERKIIEDTVVPFTVSSSSADQLSTSSSMTEGSGTMNKI  
 DLGNCQDEKQDRRWKKSFGQDDSDLLLKTRESDRLEEKGSLTEGALAHSGNPVSKGV  
 HEDHQLDTEAGAPHCGTNPQLAQDPSQNQQTSNPHTHSSSEDKPKTLPLDKSINHQIES  
 PSERRKKSPREHFQAGPFSPCSPTPPGQSPNRSISGKKLCSSCGLPLGKGAAMIETLN  
 LYFHIQCFRCGICKGQLGDAVSGTDVRIRNGLLNCNDCYMRSRSAGQPTTL

SEQ ID No: 136

MAAEWASRFLWATLLIPAAAVYEDQVGKFDWRQQYVGKVKFASLEFSPGSKKLVA  
 TEKNVIAALNSRTGEILWRHVDKGTAEGAVDAMLLHGQDVITVSNGGRIMRSWETNIGG  
 LNWEITLDGSFQALGLVGLQESVRYIAVLKKTTLALHHLSSGHLKWVEHLPESDSIHQY  
 MVYSYSGGVVWALGVVPFSHVNIKFNVEDGEIVQQVRVSTPWLQHLSGACGVVDEA  
 VLVCPDPSSRSLQTLALETEWELRQIPLQSLDLEFGSGFQPRVLPTQPNPVDASRAQFF  
 LHLSPSHYALLQYHYGTLSLLKNFPQTALVSFATTGEKTVAAVMACRNEVQKSSSSSEDG  
 SMGSFSEKSSSKDSLACFNQTYTINLYLVETGRRLDITTFSLQSGTRPERLYIQVFLK  
 KDDSVGYRALVQTEDHLLLFLQQLAGKVVLWSREESLAEVVCMVDLPLTGAQAELE  
 GEFGKKADGLLGMFLKRLSSQLILLQAWTSHLWKMFYDARKPRSQIKNEINIDTLARDEF  
 NLQKMMVMVTASGKLFGIESSSGTILWKQYLPNVKPDSSFKLMVQRTTAHFPHPPQCT  
 LLVKDKESGMSSLYVFNPFGKWSQVAPPVLKRPILOSLLLPVMDQDYAKVLLLIDDEYK  
 VTAFPATRNVLRLHELAPSIFFYLVDAAEQGRLCGYRLRKDLTTLSWELTIPPEVQRIV  
 KVKGKRSSEHVHSQGRVMGDRSVLYKSLNPNLLAVVTESTDAHHERTFIGIFLIDGVTG  
 RIIHSSVQKKAKGPVHIVHSENWVYQYWNTKARRNEFTVLELYEGTEQYNATAFSSLD  
 RPQLPQVLQQSYIFPSSISAMEATITERGITSRHLLIGLPSGAILSLPKALLDPRRPEIPTE  
 QSREENLIPYSPDVQIHAERFINYNQTVSRMRGIYTAPSGLESTCLVVAYGLDIYQTRVY  
 PSKQFDVLKDDYDYVLISSVLFGLVFATMITKRLAQVKLLNRAWR

SEQ ID No: 137

MERPWGAADGLSRWPHGLGLLLLLQLLPPSTLSQDRLDAPPPPAAPLPRWSGPIGVS  
WGLRAAAAGGAFPRGGRWRRSAPGEDEECGRVRDFVAKLANNTHQHVFDDLGRGSVS  
LSWVG DSTGVILVLTTFHVPLVIMTFGQSKLYRSEDYGKNFKDITDLINNTFIRTEFGMAI  
GPENSGKVVLTAEVSGGSRGGRIFRSSDFAKNFVQTDLPFHPLTQMMYSPQNSDYLLA  
LSTENGLWVSKNFGGKWEEIHKAVCLAKWGSDNTIFFTTYANGSCKADLGALELWRTS  
DLGKSFKTIGVKIYSFGLGGRFLFASVMADKDTTRRIHVSTDQGD TWSMAQLPSVGQE  
QFYSILAANDDMVFMHVDEPGDTGFGTIFTSDDRGIVYSKSLDRHLYTTTGGETDFTNV  
TSLRGVYITSVLSEDNSIQTMITFDQGGRWTHLRKPENSECDATAKNKNECSLHIHAS  
SISQKLNVPMAPLSEPNAVGI VIAHGSVGDAISVMVPDVYISDDGGYSWTKMLEGPHY  
TILDSGGIIVAIEHSSRPINVIKFSTDEGQCWQTYTFTRDPIYFTGLASEPGARSMNISIWG  
FTESFLT SQWVSYTIDFKDILERNCEEKDYTIWLAHSTD PEDYEDGCILGYKEQFLRLRK  
SSMCQNGRDYVVT KQPSICLCSLEDFLCDFGYR PENDSKCVEQPELK GHDLEFCLYG  
REEHLTTNGYRKIPGDKCQGGVNPVREVKDLKKKCTSNFLSPEKQNSKSN SVPIILAIVG  
LMLVTVVAGVLIVKKYVCGGRFLVHRYSVLQQHAEANGVDGVDALDTASHTNKSGYHD  
DSDEDLLE

SEQ ID No: 138

MLTFMASDSEEEVCDERTSLMSAESPTPRSCQEGRQGPEDGENTAQWRSQEN EEDG  
EEDPD RYVCSGVPGRPPGLEEEELTKYGAKHVIMLFVPVTL CMIVVATIKSVRFYTEKN  
GQLIYTPFTEDTPSVGQRLLNSVLNTLIMISVIVVMTIFLVVLYKYRCYKFIHGWLIMSSLM  
LLFLFTYIYLGEVLKTYNVAMDYPTLLLTVWNFGAVGMVCIHWKGPLVLQQAYLIMISAL  
MALVFIKYLPEWSAWVILGAISVYDLVAVLCPKGPLRMLVETAQERNEPIFPALIYSSAMV  
WTVGMAKLD PSSQ GALQLPYDPEMEEDSYDSFGEPSYPEVFEPPLTGYPGEELEEEE  
ERGVKLGLGDFIFYSVLVGKAAATGSGDWNTTLACFVAILIGLCLTLLLAVFKKALPALPI  
SITFGLIFYFSTDNLVRPFMDTLASHQLYI

SEQ ID No: 139

MGSGPLSLPLALSPPRLLLLLLLLSLLPVARASEAEHRLFERLFEDYNEIIRPVANVSDPVII  
HFEVSMSQLVKVDEVNQIMETNLWLKQIWNDYKLKWNPSDYGGAEFMRVPAQKIWKP  
DIVLYNNAVGDFQVDDKTKALLKYTGEVTWIPPAIFKSSCKIDVTYFPFDYQNCTMKFGS  
WSYDKAKIDLVLIGSSMNLKDYWESGEWAIKAPGYKHDIKYNCC EEIYPDITYSLYIRRL  
PLFY TINLIIPCLLISFLT VLVFYLP SDCGEKVTLCISVLLSLTVFLLVITETIPSTSLVIPLIGEY  
LLFTMIFVTL SIVITV FVLNVHYRTP THTMP SWVKTVFLNLLPRVMFMTRPTSNEGNAQ  
KPRPLYGAELSNLNCFSRAESKGCKEGYPCQDGMCGYCHHRRIKISNFSANLTRSSSS

ESVDAVLSLSALSPEIKEAIQSVKYIAENMKAQNEAKEEQKAQEIQQLKRKEKSTETSDQ  
EPGL

SEQ ID No: 140

MSSAPRRPAKGADSFCTPEPESLGPGTPGFPEQEEDELHRTLGVVERFEEILQEAGSRG  
GEEPGRSYGEEDFEYHRQSSHHIHHPLSTHLPPDARRRKTPQGPGRKPRRRPGASPT  
GETPTIEEGEEDEDEASEAEGARALTQPSPVSTPSSVQFFLREDDSDRKAERTSPSSP  
APLPHQEATPRASKGAQAGTQVEEAEEAEAVAVASGTAGGDDGGASGRPLPKAQPGH  
RSYNLQERRRIGSMTGAEQALLPRVPTDEIEAQTLATADLDMKSHRFEDVPGVRRHLV  
RKNAKGSTQSGREGREPGPTPRARPRAPHKPHEVFVELNELLLDKNQEPQWRETAR  
WIKFEEDVEEETERWGKPHVASLSFRSLELRRTLAHGAVLLDLDDQOTLPGVAHQVVE  
QMVISDQIKAEDRANVLRALLKHSHPSDEKDFSFPNISAGSLGSLLGHHHGQGAESD  
PHVTEPLMGGVPETRLEVERERDVPPPAPPAGITRSKSKHELKLEKIPENAEATVVLVG  
CVEFLSRPTMAFVRLREAVELDAVLEVPVPVRFLFLLGPSSANMDYHEIGRSISTLMSD  
KQFHEAAYLADEREDLLTAINAFLDCSVLPPSEVQGEELLRSVAHFQRQMLKKREEQG  
RLLPTGAGLEPKSAQDKALLQMVEAAGAAEDDPLRRTGRPFGGLIRDVRRRYPHYLS  
FRDALDPQCLAAVIFIYFAALSPAITFGGGLGEKTQDLIGVSELMSTALQGCVFCLLGAQ  
PLLVIGFSGPLLVFEEAFFSFCSSNHLEYLVGRVWIGFWLVFLALLMVALEGSFLVRFVS  
RFTQEIFAFLISLIFIYETFYKLVKIFQEHPLHGCSASNSSEVDGGENMTWAGARPTLGPG  
NRSLAGQSGQGKPRGQPNTALLSLVLMAGTFFIAFFLRKFKNRFFPGRIRRVIGDFGV  
PIAILIMVLVDYSIEDTYTQKLSVPSGFSVTAPEKRGWVINPLGEKSPFPVWMMVASLLP  
AILVFILIFMETQITTLISKKERMLQKGSGFHLDLLIVAMGGICALFGLPWLAAATVRSVT  
HANALTVMSKAVAPGDKPKIQEVKEQRTVGLLVALLVGLSIVIGDLLRQIPLAVLFGIFLY  
MGVTSLNGIQFYERLHLLLMPPKHHPDVTYVKKVRTLRMHLFTALQLLCLALLWAVMST  
AASLAFFFILITVPLRMVVLTRIFTDREMKCLDANEAEPVFDEREGVDEYNEMPMPV

SEQ ID No: 141

MGKGGNQGEAAEREVSPTFSWEEIQKHNLRTDRWLVIDRKVYNITKWSIQHPGGQ  
RVIGHYAGEDATDAFRAHPDLEFVGKFLKPLLIGELAPEEPSQDHGKNSKITEDFRALR  
KTAEDMNLFKTNHVFFLLLLAHIIALESIAWFTVFYFGNGWIPTLITAFVLATSQAQAGWL  
QHDYGHLSVYRKPKWNHLVHKFVIGHLKGASANWWNHRHFQHHAKPNIFHKDPDVNM  
LHVFLGEWQPIEYGKKKLKYLPHYHQHEYFFLIGPPLLIPMYFQYQIIMTMIVHKNWVDL  
AWAVSYYIRFFITYIPFYGILGALLFLNFIRFLESHWFVWVTQMNHIVMEIDQEAYRDWFS



SQLTATCNVEQSFFNDWFSGHLNFQIEHHLFPTMPRHNHKKIAPLVKSLCAKHGIEYQE  
KPLLRALLDIIRSLKKSGKLWLDAYLHK

SEQ ID No: 142

MERSGWARQTFLALLLGATLRARAAAGYYPRFSPFFFLCTHHGELEGDGEQGEVLISL  
HIAGNPTYYPVGQEYHVTISTSTFFDGLLVTGLYTSTSVQASQSIGGSSAFGFGIMSDHQ  
FGNQFMCSVVASHVSHLPTTNLSFIWIAPPAGTGCVNFMATATHRGQVIFKDALAQQLC  
EQGAPTDVTVHPLAEIHSDSIILRDDFDSYHQLQLNPNIWVECNNCETGEQCGAIMHG  
NAVTFCEPYGPRELITTGLNTTTASVLQFSIGSGSCRFSYSDPSIIVLYAKNNSADWIQLE  
KIRAPSNVSTIIHILYLPEDAKGENVQFQWKQENLRVGEVYEACWALDNILIINSAHRQVV  
LEDSLDPVDTGNWLFPPGATVKHSCQSDGNSIYFHGNEGSEFNFATTRDVDLSTEDIQ  
EQWSEEFESQPTGWDVLGAVIGTECGTIESGLSMVFLKDGERKLCTPSMDTTGYGNLR  
FYFVMGGICDPGNSHENDIILYAKIEGRKEHITLDTLSYSSYKVPSLVSVVINPELQTPATK  
FCLRQKNHQGHNRNVWAVDFFHVLPVLPSTMSHMIQFSINLGCGTHQPGNSVSLEFST  
NHGRSWSLLHTECLPEICAGPHLPHSTVYSSSENYSGWNRITIPNAALTRNTRIRWRQ  
TGPILGNMWAIDNVYIGPSCLKFCSGRGQCTRHGCKCDPGFSGPACEMASQTFPMFIS  
ESFGSSRLSSYHNFYSIRGAEVSFSGCVLASGKALVFNKEGRRQLITSFLDSSQSRFLQ  
FTLRLGSKSVLSTCRAPDQPGEGVLLHYSYDNGITWKLEHYSYLSYHEPRIISVELPGD  
AKQFGIQFRWWQPYHSSQREDVWAIDEIIMTSVLFNSISLDFTNLVEVTQSLGFYLGNV  
QPYCGHDWTLCFTGDSKLASSMRYVETQSMQIGASYMIQFSLVMGCGQKYTPHNDN  
QVKLEYSTNHGLTWHLVQEECLPSMPSCQEFTSASIYHASEFTQWRRVIVLLPQNDN  
SATRFRWSQSYTAQDEWALDSIYIGQQCPNMCSGHGSCDHGICRCDQGYQGGLCH  
PEAALPSTIMSDFENQNGWESDWQEVIGGEIVKPEQGCQGVISSGSSLYFSKAGKRQLV  
SWDLDTSWVDFVQFYIQIGGESASCNKPDSREEGVLLQYSNNGGIQWHLLAEMYFSDF  
SKPRFVYLELPAAAKTPCTRFRWWQPVFSGEDYDQWAVDDIILSEKQKQIIPVINPTLP  
QNFYEKPAFDYPMNQMSVWLMLANEGMVKNETFCAATPSAMIFGKSDGDRFAVTRDL  
TLKPGYVLQFKLNIGCANQFSSTAPVLLQYSHDAGMSWFLVKEGCPASAGKGCEGNS  
RELSEPTMYHTGDFEEWTRITIVIPRSLASSKTRFRRWIQESSSQKNVPPFGLDGVYISEP  
CPSYCSGHGDCISGVCFCDLGYTAAQGTCVSNVPHNEMFDRFEGKLSPLWYKITGA  
QVGTGCGTLNDGKSLYFNGPGKREARTVPLDTRNIRLVQFYIQIGSKTSGITCIKPRTRN  
EGLIVQYSNDNGILWHLLRELD FMSFLEPQIISIDLPQDAKTPATAFRWWQPQHKGKHA  
QWALDDVLIGMNDSSQTGFQDKFDGSIDLQANWYRIQGGQVDIDCLSMDTALIFTENIG  
KPRYAETWDFHVSASTFLQFEMSMGCSKPFSNSHSVQLQYSLNNGKDWHLVTEECVP  
PTIGCLHYTESSIYTSERFQNWKRITVYLPLSTISPRTRFRRWIQANYTVGADSWAIDNVVL

ASGCPWMCSGRGICDAGRCVCDRGFGGPYCVPVVPLPSILKDDFNGNLHPDLWPEVY  
GAERGNLNGETIKSGTSLIFKGEGLRMLISRDLDCNTMYVQFSLRFIAKSTPERSHSILL  
QFSISGGITWHLMDDEFYFPQTTNILFINVPLPYTAQTNATRFRLWQPYNNGKKEEIWIVD  
DFIIDGNNVNNPVMLLDTFDFGPREDNWWFFYPGGNIGLYCPYSSKGAPEEDSAMVFVS  
NEVGEHSITTRDLNVNENTIIQFEINVGCSTDSSSADPVRLEFSRDFGATWHLLLPLCYH  
SSSHVSSLCSTEHHPSSTYYAGTMQGWRREVHFGKLHLCGSRFRWYQGFYPAGS  
QPVTWAIDNVYIGPQCEEMCNGQGSCINGTKCICDPGYSGPTCKISTKNPDKDDFEG  
QLESDRFLMSGGKPSRKCGILSSGNNLFFNEDGLRMLMTRDLDSLHARFVQFFMRLG  
CGKGVDPDRSQPVLLQYSLNGGLSWSLLEFLFSNSSNVGRYIALEIPLKARSGSTRLR  
WWQPSENGHFYSPWVIDQILIGGNISGNTVLEDDFTTLDNRKWLHPGGTKMPVCGST  
GDALVFIEKASTRYVVSTDVAVNEDSFLQIDFAASCSVTDSCYAIELEYSVDLGLSWHPL  
VRDCLPTNVECSRYHLQRILVSDTFNKWTRITLPLPPYTRSQAATFRFRWHQPAPFDKQQ  
TWAIDNVYIGDGCIDMCSGHGRCIQGNCVCDEQWGGLYCDDPETSLEPTQLKDNFNRA  
PSSQNWLTVNGGKLSTVCGAVASGMALHFSGGCSRLLVTVDLNLTNAEFIQFYFMYGC  
LITPNNRNQGVLLSEYVNGGITWNLLMEIFYDQYSKPGFVNILLPPDAKEIATFRFRWWQP  
RHDGLDQNDWAIDNVLISGSADQRTVMLDTFSSAPVPQHERSPADAGPVGRIAFDMFM  
EDKTSVNEHWLFDHDDCTVERFCDSPPDGVMLCGSHDGREVYAVTHDLTPTEGWIMQFK  
ISVGCKVSEKIAQNIHVQYSTDFGVSWNYLVPQCLPADPKCSGSVSQPSVFFPTKGW  
KRITYPLPESLVGNPVRFRFYQKYSDMQWAIDNFYLGPGCLDNCRGHGDCLREQCICD  
PGYSGPNCYLTHTLKTKERFDSEEIKPDLWMSLEGGSTCTECGILAEDTALYFGGST  
VRQAVTQDLDLRGAKFLQYWGRIGSENNMTSCHRPICRKEGVLLDYSTDGGITWTLLH  
EMDYQKYISVRHDYILLPEDALTNTTRLRWWQPFVISNGIVVSGVERAQWALDNILIGGA  
EINPSQLVDTFDDEGTSHEENWSFYFNAVRTAGFCGNPSFHLWPNKKKDKTHNALSS  
RELIIQPGYMMQFKIVVGCEATSCGDLHSVMLEYTKDARSDSWQLVQTQCLPSSSNSIG  
CSPFQFHEATIYNSVNSSSWKRITIQLPDHSVSSSATQFRWIQKGEETEKQSWAIDHVIYIG  
EACPKLCSGHGYCTTGAICICDESFGGDDCSVFSHDLPSYIKDNFESARVTEANWETIQ  
GGVIGSGCGQLAPYAHGDSLYFNGCQIRQAATKPLDLTRASKIMFVLQIGSMSQTDSCN  
SDLSGPHAVDKAVLLQYSVNNGITWHVIAQHQPDKFTQAQRVSYNVPLEARMKGVLLR  
WWQPRHNGTGHDQWALDHVEVVLVSTRKQNYMMNFSRQHGLRHFYNRRRRSLRRY  
P

SEQ ID No: 143

MAEQTYSWAYSLVDSSQVSTFLISILLIVYGSFRSLNMDFENQDKEKDSNSSSGSFNGE  
QEPIIGFQPMDSRARFLPMGACVSLLVMFFFFDSVQVVFTICTAVLATIAFAFLLLPMCO

YLTRPCSPQNKISFGCCGRFTAAELLSFSLSVMLVLIWVLTGHWLLMDALAMGLCVAMI  
AFVRLPSLKVSCLLLSGLLIYDVFWVFFSAYIFNSNVMVKVATQPADNPLDVLSRKLHLG  
PNVGRDVPRLSLPGKLVFPSSTGSHFSMLGIGDIVMPGLLLCFVLRDNYKKQASGDSC  
GAPGPANISGRMQKVSYPFHCTLIGYFVGLLTATVASRIHRAAQPALLYLVPFTLLPLLTM  
AYLKGDRLRRMWSEPFHSSSSSRFLEV

SEQ ID No: 144

MAEPRQEFVEMEDHAGTYGLGDRKDQGGYTMHQDQEGD TDAGLKESPLQTPTEDGS  
EPPGSETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLE  
DEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKQGQANATRIP  
AKTPPAPKTPPSSGEPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPTREP KKVAVVR  
TPPKSPSSAKSRLQTAPVPMPLKKNVSKIGSTENLKHQPGGGKVQIINKKLDLSNVQS  
KCGSKDNIKHVPGGGSVQIVYKPVDSLKVTSKCGSLGNIHHKPGGGQVEVKSEKLDKF  
DRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAKTDHGAEIVYKSPVVSGDTSR  
HLSNVSSSTGSIDMVDSPQLATLADEV SASLAKQGL

SEQ ID No: 145

MDKNELVQKAKLAEQAERYDDMAACMKSVTEQGAELSNEERNLLSVAYKNVVGARRS  
SWRVVSSIEQKTEGAEEKQQMAREYREKIETELRDICNDVLSLLEKFLIPNASQAESKVF  
YLKMKGDYYRYLAEVAAGDDKKGIVDQSQQAYQEAFEISKKEMQPTHPIRLGLALNFSV  
FYIEILNSPEKACSLAKTAFDEAIAELDTLSEESYKDSTLIMQLLRDNLT LWTSQTQGDEA  
EAGEGGEN

SEQ ID No: 146

MSGGVYGGDEVGALVFDIGSYTVRAGYAGEDCPKVDFPTAIGMVVERDDGSTLMEIDG  
DKGKQGGPTYIIDTNALRVPRENMEASPLKNGMVEDWDSFQAILDHTYKMHVKSEAS  
LHPVLMSEAPWNTRAKREKLTLMFEHYNIPAFFLCKTAVLTAFANGRSTGLILD SGATH  
TTAIPVHDGYVLQQGIVKSPLAGDFITMQCRELFQEMNIELVPPYMIASKEAVREGSPAN  
WKRKEKLPQVTRSWHNYMCNCVIQDFQASVLQVSDSTYDEQVAAQMPTVHYEFPNG  
YNCDFGAERLKIPEGLFDPSNVKGLSGNTMLGVSHVVTTSVGMCDIDIRPGLYGSVIVA  
GGNTLIQSFTDRLNRELSQKTPPSMRLKLIANNTTVERRFSSWIGGSILASLGTFQQMWI  
SKQEYEEGGKQCVERKCP

SEQ ID No: 147



MAFVATQGATVVDQTTLMKKYLQFVAALTDVNTPDETKLKMMQEVSENFENVTSPOQY  
 STFLEHIIPRFLTFLQDGEVQFLQEKPAQQLRKLVLLEIIHRIPTNEHLRPHTKNVLSVMFRF  
 LETENEENVLICLRIIIELHKQFRPPITQEIHHFLDFVKQIYKELPKVVNRYFENPQVIPENT  
 VPPPEMVGMITTIAVKVNPEREDSETRTHSIIPRGSLSLKVLAELPIIVVLMYQLYKLNHN  
 VVAEFVPLIMNTIAIQVSAQARQHKLYNKELYADFIAAQIKTSLFLAYIIRIYQELVTKYSQQ  
 MVKGMQLLSNCPAETAHLRKELLIAAKHILTTTELNRNQFPCMDKLFDESILIGSGYTARE  
 TLRPLAYSTLADLVHHVRQHLPLSDLSLAVQLFAKNIDDESLPSSIQTMSCKLLLNLVDCI  
 RSKSEQESGNGRDVLMRMLEVFVLKFHTIARYQLSAIFKKCKPQSELGAVEAALPGVPT  
 APAAPGPAPSPAPVPAPPPPPPPPPATPVTAPVPPFEKQGEKDKEDKQTFQVTDQR  
 SLVKTLCVCGVKTITWGITSCKAPGEAQFIPNKQLQPKETQIYIKLVKYAMQALDIYQVQIA  
 GNGQTYIRVANCQTVRMKEEKEVLEHFAGVFTMMNPLTFKEIFQTTVPYMVERISKNYA  
 LQIVANSFLANPTTSALFATILVEYLLDRLPEMGSNVELSNLYLKLFLVFGSVSLFAAEN  
 EQMLKPHLHKIVNSSMELAQTAKPEYNYFLLLRLFRSIGGGGSHDLLYQEFPLLPNLLQ  
 GLNMLQSGLHKQHMKDLFVELCLTVPVRLSSLLPYLPMLMDPLVSALNGSQTLSQGL  
 RTLELCVDNLQPDFLYDHIQPVRAELMQALWRTLNRNPADSISHVAYRVLGKFGGSRNRK  
 MLKESQKLHYVVTEVQGPSITVEFSDCKASLQLPMEKAIETALDCLKSANTEPYRRQA  
 WEVIKCFVAMMSLEDNKHLYQLLAHPNFTEKTIPNVIISHRYKAQDTPARKTFEQALT  
 GAFMSAVIKDLRPSALPFVASLIRHYTMVAVAQQCGPFLLPCYQVGSQPSTAMFHSEEN  
 GSKGMDPLVLIDAIAICMAYEEKELCKIGEVALAVIFDVASIILGSKERACQLPLFSYIVERL  
 CACCYEQAWYAKLGGVVSIFLMEERLPLTWVLQNNQQTFLKALLFVMMDLTGEVSNGAV  
 AMAKTTLEQLLMRCATPLKDEERAEEIVAAQEKSFHHVTHDLVREVTSPNSTVRKQAM  
 HSLQVLAQVTGKSVTVIMEPHKEVLQDMVPPKKHLLRHQPANAQIGLMEGNTFCTTLQ  
 PRLFTMDLNVVEHKVFYTELLNLCEAEDSALTCLPCYKSLPSLVPLRIAALNALAACNYLP  
 QSREKIIAALFKALNSTNSELQEAGEACMRKFLEGATIEVDQIHTHMRPLLMLG DYRSL  
 TLNVVNRLTSVTRLFPNSFNDKFCDQMMQHLLRKWMEVVVITHKGGQRSDGNEMKICS  
 AIINLFHLIPAAPQTLVKPLLEVVMKTERAMLIEAGSPFREPLIKFLTRHPSQTVELFMMEA  
 TLNDPQWSRMFMSFLKHKDARPLRDVLAANPNRFITLLLPGGAQTAVRPGSPSTSTMR  
 LDLQFQAIKIISIIVKNDDSWLASQHSLSVSQLRRVWVSENFQERHRKENMAATNWKEPK  
 LLAYCLLNYCKRNYGDIELLFQLLRAFTGRFLCNMTFLKEYMEEEEIPKNYSIAQKRALFFR  
 FVDFNDPNFGDELKAKVLQHILNPAFLYSFEKGEQEQLLGPPNPPEGDNPESTITSVFITKV  
 LDPEKQADM LDSLRIYLLQYATLLVEHAPHHHHDNNKNRNSKLRRLMTFAWPCLLSKAC  
 VDPACKYSGHLLLAHIIAKFAIHKKIVLQVFHSLKHAHAMEARAIVRQAMAILTPAVPARM  
 EDGHQMLTHWTRKIIVEEGHTVPQLVHILHLIVQHFKVYYPVRHHLVQH MV SAMQRLGF  
 TPSVTIEQRRLAVDLSEVVIKWELQRIKDQQPDSDMDPNSSGEGVNSVSSSIKRGLSVD



SAQEVKRFRTATGAISAVFGRSQSLPGADSLAKPIDKQHTDTVVNFLIRVACQVNDNT  
NTAGSPGEVLSRRCVNLLKTALRPDMWPKSELKLQWFDKLLMTVEQPNQVNYGNICT  
GLEVLSFLLTVLQSPAILSSFKPLQRGIAACMTGNTKVLRAVHSLLSRLMSIFPTEPSTS  
SVASKYEELECLYAAVGKVIYEGLTNYEKATNANPSQLFGTLMILKSACSNNPSYIDRLIS  
VFMRSLOKQMVREHLNPQAASGSTEATSGTSELVMLSLELVKTRLAVMSMEMRKNFIQAI  
LTSLEKSPDAKILRAVVKIVEEWVKNNSPMAANQTPTLREKSILLVKMMTYIEKRFPEDL  
ELNAQFLDLVNYVYRDETLSGSELTAKLEPAFLSGLRCAQPLIRAKFFEVDNSMKRRV  
YERLLYVTCSQNWEAMGNHFWIKQCIELLAVCEKSTPIGTSCQGAMLPSITNVINLADS  
HDRAAFAMVTHVKQEPRERENSESKEEDVEIDIELAPGDQTSTPKTKELSEKDIGNQLH  
MLTNRHDKFLDTLREVKTGALLSAFVQLCHISTTLAEKTWVQLFPRLWKILSDRQQHAL  
AGEISPFLCSGSHQVQRDCQPSALNCFVEAMSQCVPPIPIRPCVLKYLKTHNLWFRST  
LMLEHQAFEKGLSLQIKPKQTTEFYEQESITPPQQEILDSLAELYSLLQEEDMWAGLWQ  
KRCKYSETATAIAYEQHGFFEQAQESYEKAMDKAKKEHERSNASPAIFPEYQLWEDHW  
IRCSKELNQWEALTEYGQSKGHINPYLVLECAWRVSNWTAMKEALVQVEVSCPKEIMA  
WKVNMYRGYLAICHPEEQQLSFIERLVEMASSLAIREWRRLPHVVSHVHTPLLQAAQQII  
ELQEAAQINAGLQPTNLGRNNSLHDMKTVVKTWRNRLPIVSDDL SHWSSIFMWRQH HY  
QAIVTAYENSSQHDPSSNNAMLGVHASASAIQYGKIARKQGLVNVALDILSRIHTIPTVPI  
VDCFQKIRQQVKCYLQLAGVMGKNECMQGLEVIESTNLKYFTKEMTAEFYALKGMFLA  
QINKSEEANKAFSAAVQMHDVLVKAWAMWGDYLENIFVKERQLHLGVSAITCYLHACR  
HQNESKSRKYLAKVLWLLSFDDDKNTLADAVDKYCIGVPPIQWLAWIPQLLTCLVGSEG  
KLLNLISQVGRVYPQAVYFPIRTLYLTLKIEQRERYKSDPGPIRATAPMWRC SRIMHMQ  
RELHPTLLSSLEGIVDQMWWFRENWHEEVLRLQLQQGLAKCYSVAFEKSGAVSDAKITP  
HTLNFVKKLVSTFGVGLENVSNVSTMFSSAASESLARRAQATAQDPVFQKLKGQFTTD  
FDFSVP GSMKLHNLISK LKKWIKILEAKTKQLPKFFLIEEKCRFLSNFSAQTAEVEIPGEFL  
MPKPTHYYIKIARFMPRVEIVQKHNTAARRLYIRGHNGKIYPYLV MNDACLTESRREERV  
LQLLRLLNPCLEKRKETT KRHLFFTVPRVVAVSPQMRLVEDNPSSLSLVEIYKQRC AKK  
GIEHDNPISRYYDRLATVQARGTQASHQVLRDILKEVQSNMVPRSMLKEWALHTFPNAT  
DYWTFRKMFTIQLALIGFAEFVLHLNRLNPEMLQIAQDTGKLVN VAYFRFDINDATGD LDA  
NRPVPFRLTPNISEFLT TIGVSGPLTASMIAVARCF AQPNFKVDGILKTVLRDEIIAWHKKT  
QEDTSSPLSAAGQPENMDSQQLVSLVQKAVTAIMTRLHNLAQFEGGESKVNTLVAAAN  
SLDNLCRMDPAWHPWL

MATGADV RDILELGGPEGDAASGTISKKDIINPDKKKSKKSSETLTfKRPEGMHREVYAL  
LYSDKKQVLEDAPLLPSDTGQGYRTVKAKLGSKKVRPWKWMPFTNPARKDGAMFFH  
WRRAAEEGKDYPFARFNKTVQVPVYSEQEYQLYLHDDAWTKAETDHLFDLSRRFDLR  
FVVIH DRYDHQQFKKRSVEDLKERYYHICAKLANVRAVPGTDLKIPVFDAGHERRRKEQ  
LERLYNRTPEQVAEEEEYLLQELRKIEARKKEREKRSQDLQKLITAADTTAEQRRTERKAP  
KKKL P QKKEAEKPAVPETAGIKFPDFKSAGVTLRSQRMKLPSSVGQKKIKALEQMLLEL  
GVELSPTPTEELVHMFNELRSDLVLLYELKQACANCEYELQMLRHRHEALARAGVLGG  
PATPASGPGPASAEP AVTEPGLGPD PKDTIIDVVGAPLTPNSRKRRESASSSSSVKKAK  
KP

SEQ ID No: 149

MHHGTGPQNVQHQLQRSRACPGSEGEEQPAHPNPPPSPAAPFAPSASPSAPQSPSY  
QIQQLMNRS PATGQNVNITLQSVGPVVGGNQQITLAPLPLPSPTSPGFQFSAQPRRFEH  
GSPSYIQVTSPLSQQVQTQSPTQPSPGPGQALQNV RAGAPGPGLGLCSSSPTGGFVD  
ASVLVRQISLSPSSGGHFVFQDGSGLTQIAQGAQVQLQHPGTPITVRERRPSQPHTQS  
GGTIHHLGPQSPAAGGAGLQPLASPSHITTANLPPQISSIIQGQLVQQQQVLQGPPLPR  
PLGFERTPGVLLPGAGGAAGFGMTSPPPPTSPSRTAVPPGLSSLPLTSVGNTGMKKVP  
KKLEEIPPAPEMAQMRKQCLDYHYQEMQALKEVFKEYLIELFFLQHFQGNMMDFLAF  
KKKHYAPLQAYLRQNDLDIEEEEEEEEEEEEEKSEVINDEQQALAGSLVAGAGSTVETDL  
FKRQQAMPSTGMAEQSKRPRLEVGHQG VVFQHPGADAGVPLQQLMPTAQGGMPPTP  
QAAQLAGQRQSQQQYDPSTGPPVQNAASLHTPLPQLPGR LPPAGVPTAALSSALQFA  
QQPQVVEAQTQLQIPVKTQQPNVPIAPPSSQLPIPPSQPAQLALHVPTPGKVQVQASQ  
LSSLPQMVA STRLPVDPAPPCPRPLPTSSTSSLAPVSGSGPGPSPARSSPVNRPSSAT  
NKALSPVTSRTPGVVASAPTKPQSPAQNATSSQDSSQDTLTEQITLENQVHQRIAELRK  
AGLWSQRRLPKLQEAPRPKSHWDYLLEEMQWMATDFAQERRWKVAAAKKLVRTVVR  
HHEEKQLREERGKKEEQSRLRRIA ASTAREIECFWSNIEQVVEIKLRVELEEKRKKALNL  
QKVSRRGKELRPKGFDALQESSLD SGMSGRKRKASISLTDDEV DDEEETIEEEEEANEG  
VVDHQTELSNLAKEAELPLDLMKLYEGAFLPSSQWPRPKPDGEDTSGEEDADDCPGD  
RESRKDLVLIDSLFIMDQFKA AERMNIGKPNAKDIADVTAVAEAILPKGSARVTTSVKFNA  
PSLLYGALRDYQKIGLDWLAKLYRKNLNGILADEAGLGKTVQIIAFFAHLACNEGNWGP  
LVVVRSCNILKWELELKRWC PGLKILSYIGSHRELKAKRQEWAEPN SFHVCITSYTQFFR  
GLTAFTRVRWKCLVIDEMQRVKGMTERHWEAVFTLQSQQRLLLIDSPLHNTFLELWTM  
VHFLVPGISR PYLSSPLRAPSEESQDY YHKVVIRLHRVTQPFILRRTKRDVEKQLTKKYE  
HVLKCRLSNRQKALYEDVILQPGTQEALKSGHFVNVLSILVRLQRICNHPGLVEPRHPG

SSYVAGPLEYPSASLILKALERDFWKEADLSMFDLIGLENKITRHEAELLSKKKIPRKLME  
EISTSAAPAARPAAAKLKASRLFQPVQYGQKPEGRTVAFPSTHPPRTAAPT TASAAPQG  
PLRGRPPIATFSANPEAKAAAAPFQTSQASASAPRHQPASASSTAASPAHPAKLRAQTT  
AQAFTPGQPPPQPQAPSHAAGQSALPQRLVLPSQAQARLP SGEVVKIAQLASITGPQS  
RVAQPETPVT LQFQGSKFTLSHSQFRQFTAGQPLQLQGSVLQIVSAPGQPYLRAPGPV  
VMQTVSQAGAVHGALGSKPPAGGPPAPLTPQVGVPGRVAVNALAVGEPGTASKPAS  
PIGGPTQEEKTRLLKERLDQIYLVNERRCSQAPVYGRDLLRICALPSHGRVQWRGSLDG  
RRGKEAGPAHSYTSSSESPSELMLTLCRCGESLQDVIDRVA FVIPPVVAAPPSLRVPRP  
PPLYSHRM RILRQGLREHAAPYFQQLRQTTAPRLLQFPELRLVQFDSGKLEALAILLQKL  
KSEGRRLV LILSQMILMLDILEMFLNFHYLTYVRIDENASSEQRQELMRSFNRRDRRIFCAIL  
STHSRTTG INLVEADTVVFYDNDLNPVMDAKAQEWCDRIGRCKDIHIYRLVSGNSIEEKL  
LKNGTKDLIREVAAQ GNDYSMAFLTQRTIQELFEVYSPMDDAGFPVKAE EFVVL SQEPS  
VTETIAPKIARPFIEALKSIEYLEEDAQKSAQEGVLGPHTDALSSDSEN MPCDEEPSQLE  
ELADFM EQLTPIEKYALNYLELFHTSIEQE KERNSEDAVMTAVRAWEFWNLKT LQEREA  
RLRLEQEEAE LLYTREDAYSMEYVYEDVDGQTEVMPLWTPPTPPQDDSDIYLD SVMC  
LMEATPIPEAKLPPVYVRKERKRHKTDPSAAGRKKKQRHGEAVVPPRSLFDRATPGLL  
KIRREGKEQKKNILLKQQVPFAKPLPTFAKPTAEPGQDNPEWLISEDWALLQAVKQLEL  
PLNLTIVSPAHTPNWDLVSDVVNSCSRIYRSSKQCRNRYENVII PREEGKSKNNRPLRTS  
QIYAQDENATH TQLYTSHFDLMKMTAGKRSPPIKPLLGMNPFQKNPKHASVLAESGINY  
DKPLPPIQVASLRAERIAKEKKALADQQKAQQPAVAQPPPPQPQPPPPPPQ QPPPPPLPQ  
PQAAGSQPPAGPPAVQPQPQPQPQTQPQP VQAPAKAQPAITTGGSAAVLAGTIKTSVT  
GTSMP TGAVSGNVIVNTIAGVPAATFQSINKRLASPVAPGALTTPGGSAPAQVVHTQPP  
PRAVGSPATATPDLVSMATTQGVRAVTSVTASAVVTTNLTPVQTPARSLVPQVSQATG  
VQLPGKTITPAHFQLLRQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQT TTTTSQV  
QVPQIQGQAQSPAQIKAVGKLTPEHLIKMQKQKLQMPPQPPPPQAQSAPPQPAQVQV  
QTSQPPQQQSPQLTTVTAPRPGALLTGTTVANLQVARLTRVPTSQLQSQGQMQTQAP  
QPAQVPLPKPPVVSVPAAVVSSPGVTTLPMNVAGISVAIGQPQKAAGQTVVAQPVHMQ  
QLLKLKQQAVQQQKAIQPQAAQGPATVQQKITAQQITTPGAQQKVAYAAQPALKTQFLT  
TPISQAQKLAGAQQVQTQIQVAKLPQVVQQQTPVASIQQVASASQQASPQTVALTQAT  
AAGQQVQMIPAVTATAQVVQQKLIQQQVVTTASAPLQTPGAPNPAQVPASSDSPSQQP  
KLQMRVPAVRLKTPTKPPCQ



MSLAGGRAPRKTAGNRLSGLLEAEEDEFYQTTYGGFTEESGDDEYQGDQSDTEDEV  
 DSDFDIDEGDEPSSDGEAEPRRKRRVVTKAYKEPLKSLRPRKVNTTPAGSSQKAREEK  
 ALLPLELQDDGSDSRKSMRQSTAEHTRQTFLRVQERQQQSRRRKGPHERPLTQEEL  
 LREAKITEELNLRSLTYERLEADKKKQVHKKRKCPGPIITYHSVTVPLVGEPPKEENV  
 DIEGLDPAPSVSALTPHAGTGPVNPPARCSRTFITFSDDATFEWFPPQGRPPKVPVREV  
 CPVTHRPALYRDPVTDIPYATARAFAKIIREAYKKYITAHGLPPTASALGPGPPPPEPLPGS  
 GPRALRQKIVIK

SEQ ID No: 151

MAHRKLESVGSGMLDHRVRPGPVPHSQEPESDMELPLEGYVPEGLELAALRPESPA  
 PEEQECHNHSPDGDSSSDYVNNTSEEEDYDEGLPEEEEGITYYIRYCPEDDSYLEGMD  
 CNGEEYLAHSAHPVDTDECQEAEEWTDASAGPHPHGHEAEGSQDYPDGQLPIPEDEP  
 SVLEAHDQEEDGHYCASKEGYQDYYPEEANGNTGASPYRLRRGDGDLEDQEEDIDQI  
 VAEIKMSLSMTSITSASEASPEHGPEPGPEDSVEACPPIKASCSPSRHEARPKSLNLLPE  
 AKHPGDPQRGFKPKTRTPPEERLKWPHQVCNGLEQPRKQQRSDLNNGPVDNNNIPETK  
 KVASFPSFVAVPGPCEPEDLIDGIIFAANYLGSTQLLSERNPSKNIRMMQAEAVSRVCR  
 MQKAAKIKKKANSEGDAQTLTEVDLFISTQRIKVLNADTQETMMDHALRTISYIADIGNIV  
 VLMARRRMPPRSASQDCIETTPGAQEGKKQYKMICHVFESDAQLIAQSIGQAFSVAYQ  
 EFLRANGINPEDLSQKEYSDIINTQEMYNDLIHFSNSENCKELQLEKHKGEILGVVVVE  
 SGWGSILPTVILANMMNGGPAARSGKLSIGDQIMSINGTSLVGLPLATCQGIKGLKNQT  
 QVKLNIVSCPPVTTVLIKRPDLKYQLGFSVQNGIICSLMRGGIAERGGVRVGHRIIEINGQ  
 SVVATAHEKIVQALSNSVGEIHMKTMPAAMFRLLTGQETPLYI

SEQ ID No: 152

MTSAAPAKKPYRKAPPEHRELRLIIPGSRLEQEEPLTDAERMKLLQEENEELRRRLASA  
 TRRTEALERELEIGQDCLELELGQSREELDKFKDKFRRLQNSYASQRTNQELEDKLHT  
 LIKKAEMDRKTLDWEIVELTNKLLDAKNTINKLEELNERYRLDCNPAVQLLKCNKSHFRN  
 HKFADLPCELQDMVRKHLHSGQEAASPGPAPSLAPGAVVPTSVIARVLEKPESELLLNSA  
 QSGSAGRPLAEDVFVHVDMSSEGVPGDPASPPAPGSPTPQPNGECHSLGTARGSPEEE  
 LPLPAFEKLNPPYPTPSPPHPLYPGRRVIEFSEDKVRIPRNSPLPNCTYATRQAISLSLVEE  
 GSERARPSVPSTPASAQASPHHQPSPAPLTLASAPASSASSEEDLLVSWQRAFDVDRTP  
 PPAAVAQRTAFGRDALPELQRHFAHSPADRDEVVQAPSARPEESELELLPTEPDGSGFPR  
 EEEELNLPISPEEERQSLLPINRGTEEGPGTSHTEGRAWPLPSSSRPQRSPPKRMGVHH  
 LHRKDSLTAQAEQGNLLN



